CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for: 074439

Trade Name : NICARDIPINE HCL CAPSULES

Generic Name: Nicardipine HCL Capsules 20mg and 30mg

Sponsor : Zenith Goldline Pharmaceuticals

Approval Date: December 10, 1996

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 074439

CONTENTS

	Included	Pending Completion	Not Prepared	Not Required
Approval Letter	X			
Tenative Approval Letter				
Approvable Letter				
Final Printed Labeling	X			
Medical Review(s)				
Chemistry Review(s)	X			
EA/FONSI				
Pharmacology Review(s)				
Statistical Review(s)				
Microbiology Review(s)				
Clinical Pharmacology Biopharmaceutics Review(s)				
Bioequivalence Review(s)	X			
Administrative Document(s)				
Correspondence				

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 074439

APPROVAL LETTER

ANDA 74-439

Zenith Goldline Pharmaceuticals
Attention: Joan Janulis
140 Legrand Avenue
Northvale, NJ 07647

Dear Madam:

This is in reference to your abbreviated new drug application dated December 21, 1993, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Nicardipine Hydrochloride Capsules, 20 mg and 30 mg.

Reference is also made to your amendments dated February 10, 1994, November 15,1994, May 21, 1996, June 13, 1996, and November 27, 1996.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Nicardipine Hydrochloride Capsules, 20 mg and 30 mg to be bioequivalent and, therefore, therapeutically equivalent to those of the listed drug (Cardene®, 20 mg and 30 mg, respectively, of Syntex Laboratories, Inc.). Your dissolution testing should be incorporated into the stability and quality control programs using the same method proposed in your application.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074439

FINAL PRINTED LABELING

Zenith

NDC 0172-4289-60

NICARDIPINE HCl
CAPSULES
30 mg

100 Capsules (Lt. Blue)

CAUTION: Federal law prohibits dispensing without prescription.

Each Capsule Contains:
Nicardipine hydrochloride 30 mg

USUAL DOSAGE: One capsule 3 times a day. See package insert.

PHARMACIST:
Dispense in a tight, light-resistant container as defined in the USP. Use child-resistant closure (as required).

Store at controlled room temperature 15°-30°C (59°-86°F).

Manufactured by:
ZENITH LABORATORIES, INC., NORTHVALE, NJ 07647
0795K

N 3 0172-4289-60 4

LOT:

EXP: DEC 10 1995

Zenith

NDC 0172-4289-80

NICARDIPINE HCl
CAPSULES
30 mg

1000 Capsules (Lt. Blue)

CAUTION: Federal law prohibits dispensing without prescription.

Each Capsule Contains:
Nicardipine hydrochloride 30 mg

USUAL DOSAGE: One capsule 3 times a day. See package insert.

PHARMACIST:
Dispense in a tight, light-resistant container as defined in the USP. Use child-resistant closure (as required).

Store at controlled room temperature 15°-30°C (59°-86°F).

Manufactured by:
ZENITH LABORATORIES, INC., NORTHVALE, NJ 07647
0795K

N 3 0172-4289-80 2

LOT:

EXP: DEC 10 1995

Zenith

NDC 0172-4289-60

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N 3 0172-4289-60 4

LOT:

EXP.

Zenith

NDC 0172-4289-80

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CAPSULES
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Manufactured by:
ZENITH LABORATORIES, INC., NORTHVALE, NJ 07647

0795K

N 3 0172-4289-80 2

LOT:

EXP.

Zenith

NDC 0172-4288-60

NICARDIPINE HCl

CAPSULES

20 mg

100 Capsules (White)

CAUTION: Federal law prohibits dispensing without prescription.

Each Capsule Contains:
Nicardipine hydrochloride 20 mg

USUAL DOSAGE: One capsule 3 times a day. See package insert.

PHARMACIST:
Dispense in a tight, light-resistant container as defined in the USP. Use child-resistant closure (as required).

Store at controlled room temperature 15°-30°C (59°-86°F).

Manufactured by:
ZENITH LABORATORIES, INC., NORTHVALE, NJ 07647

0795K

N 3 0172-4288-60 7

LOT: DEC 10 1996

EXP.

Zenith

NDC 0172-4288-80

NICARDIPINE HCl

CAPSULES

20 mg

1000 Capsules (White)

CAUTION: Federal law prohibits dispensing without prescription.

Each Capsule Contains:
Nicardipine hydrochloride 20 mg

USUAL DOSAGE: One capsule 3 times a day. See package insert.

PHARMACIST:
Dispense in a tight, light-resistant container as defined in the USP. Use child-resistant closure (as required).

Store at controlled room temperature 15°-30°C (59°-86°F).

Manufactured by:
ZENITH LABORATORIES, INC., NORTHVALE, NJ 07647

0795K

N 3 0172-4288-80 5

LOT:

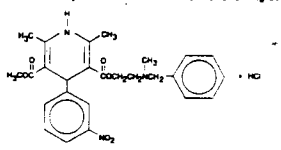
EXP. DEC 10 1996

NICARDIPINE HCl CAPSULES

DESCRIPTION

Nicardipine HCl is a calcium ion influx inhibitor (slow channel blocker or calcium channel blocker).

Nicardipine hydrochloride is a dihydropyridine structure with the IUPAC (International Union of Pure and Applied Chemistry) chemical name 2-(benzyl-methyl amino)ethyl methyl 1,4-dihydro-2,6-dimethyl-4-(*m*-nitrophenyl)-3,5-pyridinedicarboxylate monohydrochloride, and it has the following structural formula:



$C_{26}H_{29}N_3O_6.HCl$ M.W. 515.99

Nicardipine hydrochloride is a greenish-yellow, odorless, crystalline powder that melts at about 169°C. It is freely soluble in chloroform, methanol, and glacial acetic acid, sparingly soluble in anhydrous ethanol, slightly soluble in n-butanol, water, 0.01 M potassium dihydrogen phosphate, acetone, and dioxane, very slightly soluble in ethyl acetate, and practically insoluble in benzene, ether and hexane.

Each capsule, for oral administration, contains 20 mg or 30 mg nicardipine hydrochloride. In addition, each capsule contains the following inactive ingredients: edible black ink (black iron oxide, D&C Yellow No. 10 Aluminum Lake, FD&C Blue No. 1 Aluminum Lake, FD&C Blue No. 2 Aluminum Lake, FD&C Red No. 40 Aluminum Lake) magnesium stearate and pregelatinized starch. The 20 mg strength is provided in opaque white capsules composed of gelatin, silicon dioxide, sodium lauryl sulfate, and titanium dioxide as a colorant. The 30 mg strength is provided in light blue opaque capsules composed of gelatin, silicon dioxide, sodium lauryl sulfate, and, as colorants, titanium dioxide and FD&C Blue #1.

CLINICAL PHARMACOLOGY

Mechanism of Action

Nicardipine is a calcium entry blocker (slow channel blocker or calcium ion antagonist) which inhibits the transmembrane influx of calcium ions into cardiac muscle and smooth muscle without changing serum calcium concentrations. The contractile processes of cardiac muscle and vascular smooth muscle are dependent upon the movement of extracellular calcium ions into these cells through specific ion channels. The effects of nicardipine are more selective to vascular smooth muscle than cardiac muscle. In animal models, nicardipine produces relaxation of coronary vascular smooth muscle at drug levels which cause little or no negative inotropic effect.

Pharmacokinetics and Metabolism

Nicardipine is completely absorbed following oral doses administered as capsules. Plasma levels are detectable as early as 20 minutes following an oral dose and maximal plasma levels are observed within 30 minutes to two hours (mean T_{max} = 1 hour). While nicardipine is completely absorbed, it is subject to saturable first pass metabolism and the systemic bioavailability is about 35% following a 30 mg oral dose at steady state.

When nicardipine was administered one (1) or three (3) hours after a high fat meal, the mean C_{max} and mean AUC were lower (20% to 30%) than when nicardipine was given to fasting subjects. These decreases in plasma levels observed following a meal may be significant but the clinical trials establishing the efficacy and safety of nicardipine were done in patients without regard to the timing of meals. Thus the results of these trials reflect the effects of meal-induced variability.

The pharmacokinetics of nicardipine are nonlinear due to saturable hepatic first pass metabolism. Following oral administration, increasing doses result in a disproportionate increase in plasma levels. Steady state C_{max} values following 20, 30 and 40 mg doses every 8 hours averaged 36, 88 and 133 ng/mL respectively. Hence, increasing the dose from 20 to 30 mg every 8 hours more than doubled C_{max} and increasing the dose from 20 to 40 mg every 8 hours increased C_{max} more than 3-fold. A similar disproportionate increase in AUC with dose was observed. Considerable inter-subject variability in plasma levels was also observed.

Post-absorption kinetics of nicardipine are also non-linear, although there is a reproducible terminal plasma half-life that averaged 8.6 hours following 30 and 40 mg doses at steady state (TID). The terminal half-life represents the elimination of less than 5% of the absorbed drug (measured by plasma concentrations). Elimination over the first 8 hours after dosing is much faster with a half-life of 2-4 hours. Steady state plasma levels are achieved after 2 to 3 days of TID dosing (every 8 hours) and are 2-fold higher than after a single dose.

Nicardipine is highly protein bound (>95%) in human plasma over a wide concentration range.

Nicardipine is metabolized extensively by the liver; less than 1% of intact drug is detected in the urine. Following a radioactive oral dose in solution, 60% of the radioactivity was recovered in the urine and 35% in feces. Most of the dose (over 90%) was recovered within 48 hours of dosing. Nicardipine does not induce its own metabolism and does not induce hepatic microsomal enzymes.

The steady-state pharmacokinetics of nicardipine in elderly hypertensive patients (≥65 years) are similar to those obtained in young normal adults. After one week of nicardipine hydrochloride dosing at 20 mg three times a day, the C_{max}, T_{max}, AUC, terminal plasma half-life, and the extent of protein binding of nicardipine observed in healthy elderly hypertensive patients did not differ significantly from those observed in young normal volunteers.

Nicardipine plasma levels were higher in patients with mild renal impairment (baseline serum creatinine concentration ranged from 1.2 to 5.5 mg/dL) than in normal subjects. After 30 mg nicardipine hydrochloride TID at steady state, C_{max} and AUC were approximately 2-fold higher in these patients.

Because nicardipine is extensively metabolized by the liver, the plasma levels of the drug are influenced by changes in hepatic function. Nicardipine plasma levels were higher in patients with severe liver disease (hepatic cirrhosis confirmed by liver biopsy or presence of endoscopically-confirmed esophageal varices) than in normal subjects. After 20 mg nicardipine hydrochloride BID at steady state, C_{max} and AUC were 1.8 and 4-fold higher, and the terminal half-life was prolonged to 19 hours in these patients.

Hemodynamics

In man, nicardipine produces a significant decrease in systemic vascular resistance. The degree of vasodilation and the resultant hypotensive effects are more prominent in hypertensive patients. In hypertensive patients, nicardipine reduces the blood pressure at rest and during isometric and dynamic exercise. In normotensive patients, a small decrease of about 9 mmHg in systolic and 7 mmHg in diastolic blood pressure may accompany this fall in peripheral resistance. An increase in heart rate may occur in response to the vasodilation and decrease in blood pressure, and in a few patients this heart rate increase may be pronounced. In clinical studies mean heart rate at time of peak plasma levels was usually increased by 5-10 beats per minute compared to placebo, with the greater increases at higher doses, while there was no difference from placebo at the end of the dosing interval. Hemodynamic studies following intravenous dosing in patients with coronary artery disease and normal or moderately abnormal left ventricular function have shown significant increases in ejection fraction and cardiac output with no significant change, or a small decrease, in left ventricular end-diastolic pressure (LVEDP). Although there is evidence that nicardipine increases coronary blood flow, there is no evidence that this property plays any role in its effectiveness in stable angina. In patients with coronary artery disease, intracoronary administration of nicardipine caused no direct myocardial depression. Nicardipine does, however, have a negative inotropic effect in some patients with severe left ventricular dysfunction and could, in patients with very impaired function, lead to worsened failure.

"Coronary Steal", the detrimental redistribution of coronary blood flow in patients with coronary artery disease (diversion of blood from underperfused areas toward better perfused areas), has not been observed during nicardipine treatment. On the contrary, nicardipine has been shown to improve systolic shortening in normal and hypokinetic segments of myocardial muscle, and radio-nuclide angiography has confirmed that wall motion remained improved during an increase in oxygen demand. Nonetheless, occasional patients have developed increased angina upon receiving nicardipine. Whether this represents steal in those patients, or is the result of increased heart rate and decreased diastolic pressure, is not clear.

In patients with coronary artery disease nicardipine improves L.V. diastolic distensibility during the early filling phase, probably due to a faster rate of myocardial relaxation in previously underperfused areas. There is little or no effect on normal myocardium, suggesting the improvement is mainly by indirect mechanisms such as afterload reduction, and reduced ischemia. Nicardipine has no negative effect on myocardial relaxation at therapeutic doses. The clinical consequences of these properties are as yet undemonstrated.

Electrophysiologic Effects

In general, no detrimental effects on the cardiac conduction system were seen with the use of nicardipine. Nicardipine increased the heart rate when given intravenously during acute electrophysiologic studies, and prolonged the corrected QT interval to a minor degree. The sinus node recovery times and SA conduction times were not affected by the drug. The PA, AH and HV intervals* and the functional and effective refractory periods of the atrium were not prolonged by nicardipine and the relative and effective refractory periods of the His-Purkinje system were slightly shortened after intravenous nicardipine.

*PA = conduction time from high to low right atrium,
AH = conduction time from low right atrium to His bundle deflection, or AV nodal conduction time.
HV = conduction time through the His bundle and the bundle branch-Purkinje system.

Renal Function

There is a transient increase in electrolyte excretion, including sodium. Nicardipine does not cause generalized fluid retention, as measured by weight changes, although 7-8% of the patients experience pedal edema.

Effects in Angina Pectoris

In controlled clinical trials of up to 12 weeks duration in patients with chronic stable angina, nicardipine increased exercise tolerance and reduced nitroglycerin consumption and the frequency of anginal attacks. The antianginal efficacy of nicardipine (20-40 mg) has been demonstrated in four placebo-controlled studies involving 258 patients with chronic stable angina. In exercise tolerance testing, nicardipine significantly increased time to angina, total exercise duration and time to 1 mm ST segment depression. Included among these four studies was a dose-definition study in which dose-related improvements in exercise tolerance at one and four hours post-dosing and reduced frequency of anginal attacks were seen at doses of 10, 20 and 30 mg TID. Effectiveness at 10 mg TID was, however, marginal. In a fifth placebo-controlled study, the antianginal efficacy of nicardipine was demonstrated at 8 hours post-dose (trough). The sustained efficacy of nicardipine has been demonstrated over long-term dosing. Blood pressure fell in patients with angina by about 10/8 mmHg at peak blood levels and was little different from placebo at trough blood levels.

Effects in Hypertension

Nicardipine produced dose-related decreases in both systolic and diastolic blood pressure in clinical trials. The antihypertensive efficacy of nicardipine administered three times daily has been demonstrated in three placebo-controlled studies involving 517 patients with mild to moderate hypertension. The blood pressure responses in the three studies were statistically significant from placebo at peak (1 hour post-dosing) and trough (8 hours post-dosing) although it is apparent that well over half of the antihypertensive effect is lost by the end of the dosing interval. The results from placebo controlled studies of nicardipine given three times daily are shown in the following table:

	SYSTOLIC BP (mmHg)					DIASTOLIC BP (mmHg)			
Dose	Number of Patients	Mean Peak Response	Mean Trough Response	Trough/ Peak	Dose	Number of Patients	Mean Peak Response	Mean Trough Response	Trough/ Peak
20 mg	50	-10.3	-4.9	48%	20 mg	50	-10.6	-4.6	43%
	52	-17.6	-7.9	45%		52	- 9.0	-2.9	32%
30 mg	45	-14.5	-7.2	50%	30 mg	45	-12.8	-4.9	38%
	44	-14.6	-7.5	51%		44	-14.2	-4.3	30%
40 mg	50	-16.3	-9.5	58%	40 mg	50	-15.4	-5.9	38%
	38	-15.9	-6.0	38%		38	-14.8	-3.7	25%

The responses are shown as differences from the concurrent placebo control group. The large changes between peak and trough effects were not accompanied by observed side effects at peak response times. In a study using 24 hour intra-arterial blood pressure monitoring, the circadian variation in blood pressure remained unaltered, but the systolic and diastolic blood pressures were reduced throughout the whole 24 hours.

When added to beta-blocker therapy, nicardipine further lowers both systolic and diastolic blood pressure.

INDICATIONS AND USAGE

I. Stable Angina

Nicardipine HCl Capsules are indicated for the management of patients with chronic stable angina (effort-associated angina). They may be used alone or in combination with beta-blockers.

II. Hypertension

Nicardipine HCl Capsules are indicated for the treatment of hypertension. They may be used alone or in combination with other antihypertensive drugs. In administering nicardipine it is important to be aware of the relatively large peak to trough differences in blood pressure effect. (See **DOSAGE AND ADMINISTRATION**.)

CONTRAINDICATIONS

Nicardipine hydrochloride capsules are contraindicated in patients with hypersensitivity to the drug. Because part of the effect of nicardipine is secondary to reduced afterload, the drug is also contraindicated in patients with advanced aortic stenosis. Reduction of diastolic pressure in these patients may worsen rather than improve myocardial oxygen balance.

WARNINGS

Increased Angina

About 7% of patients in short term placebo-controlled angina trials have developed increased frequency, duration or severity of angina on starting nicardipine or at the time of dosage increases, compared with 4% of patients on placebo. Comparisons with beta-blockers also show a greater frequency of increased angina, 4% vs 1%. The mechanism of this effect has not been established. (See **ADVERSE REACTIONS**.)

Use in Patients with Congestive Heart Failure

Although preliminary hemodynamic studies in patients with congestive heart failure have shown that nicardipine reduced afterload without impairing myocardial contractility, it has a negative inotropic effect *in vitro* and in some patients. Caution should be exercised when using the drug in congestive heart failure patients, particularly in combination with a beta-blocker.

Beta-Blocker Withdrawal

Nicardipine is not a beta-blocker and therefore gives no protection against the dangers of abrupt beta-blocker withdrawal; any such withdrawal should be by gradual reduction of the dose of beta-blocker, preferably over 8-10 days.

PRECAUTIONS

General

Blood Pressure: Because nicardipine decreases peripheral resistance, careful monitoring of blood pressure during the initial administration and titration of nicardipine is suggested. Nicardipine, like other calcium channel blockers, may occasionally produce symptomatic hypotension. Caution is advised to avoid systemic hypotension when administering the drug to patients who have sustained an acute cerebral infarction or hemorrhage. Because of prominent effects at the time of peak blood levels, initial titration should be performed with measurements of blood pressure at peak effect (1-2 hours after dosing) and just before the next dose.

Use in patients with impaired hepatic function: Since the liver is the major site of biotransformation and since nicardipine is subject to first pass metabolism, the drug should be used with caution in patients having impaired liver function or reduced hepatic blood flow. Patients with severe liver disease developed elevated blood levels (4-fold increase in AUC) and prolonged half-life (19 hours) of nicardipine. (See **DOSAGE AND ADMINISTRATION**.)

Use in patients with impaired renal function: When nicardipine hydrochloride 20 mg or 30 mg TID was given to hypertensive patients with mild renal impairment, mean plasma concentrations, AUC, and C_{max} were approximately 2-fold higher in renally impaired patients than in healthy controls. Doses in these patients must be adjusted. (See **CLINICAL PHARMACOLOGY** and **DOSAGE AND ADMINISTRATION**.)

Drug Interactions

Beta-Blockers: In controlled clinical studies, adrenergic beta-receptor blockers have been frequently administered concomitantly with nicardipine. The combination is well tolerated.

Cimetidine: Cimetidine increases nicardipine plasma levels. Patients receiving the two drugs concomitantly should be carefully monitored.

NICARDIPINE HCl CAPSULES 0093-01

0093-01 NICARDIPINE HCl CAPSULES

Digoxin: Some calcium blockers may increase the concentration of digitalis preparations in the blood. Nicardipine usually does not alter the plasma levels of digoxin, however, serum digoxin levels should be evaluated after concomitant therapy with nicardipine is initiated.

Aluminum and Magnesium Hydroxides: Co-administration of an antacid containing 600 mg aluminum hydroxide and 300 mg magnesium hydroxide had no effect on nicardipine absorption.

Fentanyl Anesthesia: Severe hypotension has been reported during fentanyl anesthesia with concomitant use of a beta-blocker and a calcium channel blocker. Even though such interactions were not seen during clinical studies with nicardipine, an increased volume of circulating fluids might be required if such an interaction were to occur.

Cyclosporine: Concomitant administration of nicardipine and cyclosporine results in elevated plasma cyclosporine levels. Plasma concentrations of cyclosporine should therefore be closely monitored, and its dosage reduced accordingly, in patients treated with nicardipine.

When therapeutic concentrations of *furosemide, propranolol, dipyridamole, warfarin, quinidine,* or *naproxen* were added to human plasma (*in vitro*), the plasma protein binding of nicardipine was not altered.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Rats treated with nicardipine in the diet (at concentrations calculated to provide daily dosage levels of 5, 15 or 45 mg/kg/day) for two years showed a dose-dependent increase in thyroid hyperplasia and neoplasia (follicular adenoma/carcinoma). One and three month studies in the rat have suggested that these results are linked to a nicardipine-induced reduction in plasma thyroxine (T4) levels with a consequent increase in plasma levels of thyroid stimulating hormone (TSH). Chronic elevation of TSH is known to cause hyperstimulation of the thyroid. In rats on an iodine deficient diet, nicardipine administration for one month was associated with thyroid hyperplasia that was prevented by T4 supplementation. Mice treated with nicardipine in the diet (at concentrations calculated to provide daily dosage levels of up to 100 mg/kg/day) for up to 18 months showed no evidence of neoplasia of any tissue and no evidence of thyroid changes. There was no evidence of thyroid pathology in dogs treated with up to 25 mg nicardipine/kg/day for one year and no evidence of effects of nicardipine on thyroid function (plasma T4 and TSH) in man.

There was no evidence of a mutagenic potential of nicardipine in a battery of genotoxicity tests conducted on microbial indicator organisms, in micronucleus tests in mice and hamsters, or in a sister chromatid exchange study in hamsters.

No impairment of fertility was seen in male or female rats administered nicardipine at oral doses as high as 100 mg/kg/day (50 times the 40 mg TID maximum recommended antianginal or antihypertensive dose in man, assuming a patient weight of 60 kg).

Pregnancy

Pregnancy Category C: Nicardipine was embryocidal when administered orally to pregnant Japanese White rabbits, during organogenesis, at 150 mg/kg/day (a dose associated with marked body weight gain suppression in the treated doe) but not at 50 mg/kg/day (25 times the maximum recommended antianginal or antihypertensive dose in man). No adverse effects on the fetus were observed when New Zealand albino rabbits were treated, during organogenesis, with up to 100 mg nicardipine/kg/day (a dose associated with significant mortality in the treated doe). In pregnant rats administered nicardipine orally at up to 100 mg/kg/day (50 times the maximum recommended human dose) there was no evidence of embryolethality or teratogenicity. However, dystocia, reduced birth weights, reduced neonatal survival and reduced neonatal weight gain were noted. There are no adequate and well-controlled studies in pregnant women. Nicardipine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

Studies in rats have shown significant concentrations of nicardipine in maternal milk following oral administration. For this reason it is recommended that women who wish to breast-feed should not take this drug.

Pediatric Use

Safety and efficacy in patients under the age of 18 have not been established.

Use in the Elderly

Pharmacokinetic parameters did not differ between elderly hypertensive patients (≥65 years) and healthy controls after one week of nicardipine hydrochloride treatment at 20 mg TID. Plasma nicardipine concentrations in elderly hypertensive patients were similar to plasma concentrations in healthy young adult subjects when nicardipine was administered at doses of 10, 20 and 30 mg TID, suggesting that the pharmacokinetics of nicardipine are similar in young and elderly hypertensive patients. No significant differences in responses to nicardipine have been observed in elderly patients and the general adult population of patients who participated in clinical studies.

ADVERSE REACTIONS

In multiple-dose U.S. and foreign controlled short-term (up to three months) studies 1,910 patients received nicardipine alone or in combination with other drugs. In these studies adverse events were reported spontaneously; adverse experiences were generally not serious but occasionally required dosage adjustment and about 10% of patients left the studies prematurely because of them. Peak responses were not observed to be associated with adverse effects during clinical trials, but physicians should be aware that adverse effects associated with decreases in blood pressure (tachycardia, hypotension, etc.) could occur around the time of the peak effect. Most adverse effects were expected consequences of the vasodilator effects of nicardipine.

Angina

The incidence rates of adverse effects in anginal patients were derived from multicenter, controlled clinical trials. Following are the rates of adverse effects for nicardipine (N=520) and placebo (N=310), respectively, that occurred in 0.4% of patients or more. These represent events considered probably drug-related by the investigator (except for certain cardiovascular events which were recorded in a different category). Where the frequency of adverse effects for nicardipine and placebo is similar, causal relationship is uncertain. The only dose-related effects were pedal edema and increased angina.

Percent of Patients with Adverse Effects in Controlled Studies
(Incidence of discontinuations shown in parentheses)

ADVERSE EXPERIENCE	Nicardipine (N=520)	PLACEBO (N=310)
Pedal Edema	7.1 (0)	0.3 (0)
Dizziness	6.9 (1.2)	0.6 (0)
Headache	6.4 (0.6)	2.6 (0)
Asthenia	5.8 (0.4)	2.6 (0)
Flushing	5.6 (0.4)	1.0 (0)
Increased Angina	5.6 (3.5)	4.2 (1.9)
Palpitations	3.3 (0.4)	0.0 (0)
Nausea	1.9 (0)	0.3 (0)
Dyspepsia	1.5 (0.6)	0.6 (0.3)
Dry Mouth	1.4 (0)	0.3 (0)
Somnolence	1.4 (0)	1.0 (0)
Rash	1.2 (0.2)	0.3 (0)
Tachycardia	1.2 (0.2)	0.6 (0)
Myalgia	1.0 (0)	0.0 (0)
Other edema	1.0 (0)	0.0 (0)
Paresthesia	1.0 (0.2)	0.3 (0)
Sustained Tachycardia	0.8 (0.6)	0.0 (0)
Syncope	0.8 (0.2)	0.0 (0)
Constipation	0.6 (0.2)	0.6 (0)
Dyspnea	0.6 (0)	0.0 (0)
Abnormal ECG	0.6 (0.6)	0.0 (0)
Malaise	0.6 (0)	0.0 (0)
Nervousness	0.6 (0)	0.3 (0)
Tremor	0.6 (0)	0.0 (0)

In addition, adverse events were observed which are not readily distinguishable from the natural history of the atherosclerotic vascular disease in these patients. Adverse events in this category each occurred in <0.4% of patients receiving nicardipine and included myocardial infarction, atrial fibrillation, exertional hypotension, pericarditis, heart block, cerebral ischemia and ventricular tachycardia. It is possible that some of these events were drug-related.

Hypertension

The incidence rates of adverse effects in hypertensive patients were derived from multicenter, controlled clinical trials. Following are the rates of adverse effects for nicardipine (N=1390) and placebo (N=211), respectively, that occurred in 0.4% of patients or more. These represent events considered probably drug-related by the investigator. Where the frequency of adverse effects for nicardipine and placebo is similar, causal relationship is uncertain. The only dose-related effect was pedal edema.

Percent of Patients with Adverse Effects in Controlled Studies
(Incidence of discontinuations shown in parentheses)

Adverse Experience	Nicardipine (N=1390)	PLACEBO (N=211)
Flushing	9.7 (2.1)	2.8 (0)
Headache	8.2 (2.6)	4.7 (0)
Pedal Edema	8.0 (1.8)	0.9 (0)
Asthenia	4.2 (1.7)	0.5 (0)
Palpitations	4.1 (1.0)	0.0 (0)
Dizziness	4.0 (1.8)	0.0 (0)
Tachycardia	3.4 (1.2)	0.5 (0)
Nausea	2.2 (0.9)	0.9 (0)
Somnolence	1.1 (0.1)	0.0 (0)
Dyspepsia	0.8 (0.3)	0.5 (0)
Insomnia	0.6 (0.1)	0.0 (0)
Malaise	0.6 (0.1)	0.0 (0)
Other edema	0.6 (0.3)	1.4 (0)
Abnormal dreams	0.4 (0)	0.0 (0)
Dry mouth	0.4 (0.1)	0.0 (0)
Nocturia	0.4 (0)	0.0 (0)
Rash	0.4 (0.4)	0.0 (0)
Vomiting	0.4 (0.4)	0.0 (0)

Rare Events

The following rare adverse events have been reported in clinical trials or the literature:

Body as a Whole: infection, allergic reaction
Cardiovascular: hypotension, postural hypotension, atypical chest pain, peripheral vascular disorder, ventricular extrasystoles, ventricular tachycardia
Digestive: sore throat, abnormal liver chemistries
Musculoskeletal: arthralgia
Nervous: hot flashes, vertigo, hyperkinesia, impotence, depression, confusion, anxiety
Respiratory: rhinitis, sinusitis
Special Senses: tinnitus, abnormal vision, blurred vision
Urogenital: increased urinary frequency

OVERDOSAGE

Overdosage with a 600 mg single dose (15 to 30 times normal clinical dose) has been reported. Marked hypotension (blood pressure unobtainable) and bradycardia (heart rate 20 bpm in normal sinus rhythm) occurred, along with drowsiness, confusion and slurred speech. Supportive treatment with a vasopressor resulted in gradual improvement with normal vital signs approximately 9 hours post treatment.

Based on results obtained in laboratory animals, overdosage may cause systemic hypotension, bradycardia (following initial tachycardia) and progressive atrioventricular conduction block. Reversible hepatic function abnormalities and sporadic focal hepatic necrosis were noted in some animal species receiving very large doses of nicardipine.

For treatment of overdose standard measures (for example, evacuation of gastric contents, elevation of extremities, attention to circulating fluid volume and urine output) including monitoring of cardiac and respiratory functions should be implemented. The patient should be positioned so as to avoid cerebral anoxia. Frequent blood pressure determinations are essential. Vasopressors are clinically indicated for patients exhibiting profound hypotension. Intravenous calcium gluconate may help reverse the effects of calcium entry blockade.

DOSAGE AND ADMINISTRATION

Angina

The dose should be individually titrated for each patient beginning with 20 mg three times daily. Doses in the range of 20-40 mg three times a day have been shown to be effective. At least three days should be allowed before increasing the nicardipine hydrochloride dose to ensure achievement of steady state plasma drug concentrations.

Concomitant Use With Other Antianginal Agents

1. Sublingual NTG may be taken as required to abort acute anginal attacks during nicardipine therapy.
2. Prophylactic Nitrate Therapy - Nicardipine may be safely coadministered with short- and long-acting nitrates.
3. Beta-blockers - Nicardipine may be safely coadministered with beta-blockers. (See **DRUG INTERACTIONS.**)

Hypertension

The dose of nicardipine hydrochloride should be individually adjusted according to the blood pressure response beginning with 20 mg three times daily. The effective doses in clinical trials have ranged from 20 mg to 40 mg three times daily. The maximum blood pressure lowering effect occurs approximately 1-2 hours after dosing. **To assess the adequacy of blood pressure response, the blood pressure should be measured at trough (8 hours after dosing). Because of the prominent peak effects of nicardipine, blood pressure should be measured 1-2 hours after dosing, particularly during initiation of therapy.** (See **PRECAUTIONS: Blood Pressures, INDICATIONS** and **CLINICAL PHARMACOLOGY - Peak/Trough Effects in Hypertension.**) At least three days should be allowed before increasing the nicardipine dose to ensure achievement of steady state plasma drug concentrations.

Concomitant use with other Antihypertensive Agents

1. Diuretics - Nicardipine may be safely coadministered with thiazide diuretics.
2. Beta-Blockers - Nicardipine may be safely coadministered with beta-blockers. (See **DRUG INTERACTIONS.**)

Special Patient Populations

Renal Insufficiency - although there is no evidence that nicardipine impairs renal function, careful dose titration beginning with 20 mg TID is advised. (See **PRECAUTIONS.**)

Hepatic Insufficiency - Nicardipine should be administered cautiously in patients with severely impaired hepatic function. A suggested starting dose of 20 mg twice a day is advised with individual titration based on clinical findings maintaining the twice a day schedule. (See **PRECAUTIONS.**)

Congestive Heart Failure - Caution is advised when titrating nicardipine dosage in patients with congestive heart failure. (See **WARNINGS.**)

HOW SUPPLIED

Nicardipine HCl Capsules are available as white opaque capsules, imprinted with Z, "Zenith", "4288", and "20 mg", containing 20 mg nicardipine hydrochloride, packaged in bottles of 100 and 1000 capsules; and as light blue opaque capsules, imprinted with Z, "Zenith", "4289", and "30 mg", containing 30 mg nicardipine hydrochloride, packaged in bottles of 100 and 1000 capsules.

PHARMACIST: Dispense in a tight, light-resistant container as defined in the USP. Use child-resistant closure (as required).

Store at controlled room temperature 15°-30°C(59°-86°F).

CAUTION: Federal law prohibits dispensing without prescription.

MANUFACTURED BY
ZENITH GOLDLINE PHARMACEUTICALS, INC.
FT. LAUDERDALE, FL 33309

0172
5/96
01

NICARDIPINE HCl CAPSULES

NICARDIPINE HCl CAPSULES 0093-01

0093-01 NICARDIPINE HCl CAPSULES

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074439

CHEMISTRY REVIEW(S)

OFFICE OF GENERIC DRUGS
Division of Chemistry II

ANDA REVIEW

1. CHEMIST'S REVIEW NO. 3

2. ANDA # 74-439

3. NAME AND ADDRESS OF APPLICANT

Zenith Laboratories, Inc.
Attention: Joan Janulis
140 Legrand Avenue
Northvale, NJ 07647

4. LEGAL BASIS for ANDA SUBMISSION

1.30.95.

5. SUPPLEMENT(s): None

6. PROPRIETARY NAME None

7. NONPROPRIETARY NAME Nicardapine Hydrochloride Capsules

8. SUPPLEMENT(s) PROVIDE(s) FOR: N/A

9. AMENDMENTS AND OTHER DATES:

Firm:

12.21.93 - Original Application
02.10.94 - Bio Amend
11.15.94 - Bio Amend
08.08.95 - Amendment
05.21.96 - Labeling Amendment
06.13.96 - Amendments **Subject of this review**
11.27.96 - Amendment -11- LV.

FDA:

06.07.94 - N/A letter #1
04.01.96 - N/A letter #2

10. PHARMACOLOGICAL CATEGORY

Anti-hypertensive

11. Rx or OTC

R_x

12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM

Capsules

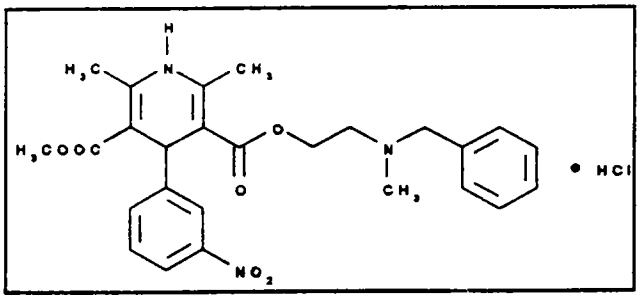
14. POTENCIES

20 and 30 mg

15. CHEMICAL NAME AND STRUCTURE

Nicardipine Hydrochloride

$C_{26}H_{29}N_3O_6.HCl$; M.W. = 515.99



2-(Benzylmethylamino)ethyl methyl 1,4-dihydro-2,6-dimethyl-4-(*m*-nitrophenyl)-3,5-pyridinedicarboxylate monohydrochloride.
CAS [54527-84-3]

16. RECORDS AND REPORTS: None

17. COMMENTS

a. DMF for NDS satisfactory, U. V. Venkataram, 10.16.96.
b. Manufacturing records are satisfactory.
c. Laboratory controls are satisfactory.
d. Labeling is satisfactory.
e. MV satisfactory - 6.13.96
f. Bioreview satisfactory, M. M. Kochhar, 5.10.95
g. Establishment inspection not acceptable - 8.2.94

18. CONCLUSIONS AND RECOMMENDATIONS

The amendment is satisfactory in chemistry and labeling. It may be approved pending satisfactory EIR.

19. REVIEWER: DATE COMPLETED:

Ubrani V. Venkataram, Ph.D. 10.16.96

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074439

BIOEQUIVALENCE REVIEW(S)

Nicardipine Hydrochloride,
Capsules, 20 mg and 30 mg
ANDA 74-439

MAY 19 1994

Zenith Laboratories Inc.
Attention: Nicholas Maselli
Department of Regulatory Affairs
140 Legrand Avenue
Northvale, NJ 07647

Dear Mr. Maselli:

Reference is made to the *in vivo* bioequivalence studies, dissolution data, and waiver request, submitted on December 21, 1993 (fasting study) and February 10, 1994 (fed-study) for nicardipine hydrochloride ANDA 74-439.

The Office of Generic Drugs/Division of Bioequivalence has reviewed this material and we have the following comments:

A. An unacceptable dissolution method was used in both submissions. Please submit dissolution data using the following Food and Drug Administration dissolution methodology:

Medium: 900 mL of 0.333*M* Citrate Buffer, pH 4.5 at 37°C

Apparatus: USP XXII apparatus 2 (Paddle) at 50 rpm

The test product should meet the following specifications:

Not less than of the labeled amount of nicardipine HCl dissolved in 30 minutes.

B. The waiver request can not be considered until the 30 mg product is found acceptable. Please resubmit your waiver request with your amendment.

You are required to take an action described under 21 CFR 314.96 which will amend this submission.

All responses and correspondence with regard to this letter should indicate the date of this letter, and be addressed to the Office of Generic Drugs/Division of Bioequivalence, HFD-650.

A representative of the Division of Bioequivalence is available to clarify this letter and to assist you with any questions; you may contact Jason A. Gross, Pharm.D., at (301) 594-2290.

Sincerely yours,

Ramakant M. Mhatre, Ph.D.
Acting Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: Date _____
HFD-632 Johnston/
HFD-650 (Mhatre, Gross, CST)
bio letter

Endorsements:

M. Kochhar
M. Park
J. Gross

DRAFT:	STM	5/10/94	X:\WPFILE\BIO\N74439D1.STU
revised:	JAG	5/11/94	X:\WPFILE\BIO\N74439D2.STU
FINAL:	STM	5/17/94	X:\WPFILE\BIO\FINAL\N74439.STU

APR 29 1994

Nicardipine Hydrochloride
Capsules, 20 mg and 30 mg
ANDA # 74-439
Reviewer: Man M. Kochhar
74439.SDW.D93

Zenith Laboratories Inc.
Northvale, N.J.
Submission Date:
December 21, 1993

Review of Bioequivalence Study, Waiver Request and Dissolution

OBJECTIVE:

The objective of this study was to compare the bioavailability of Zenith Laboratories and Syntex (Cardene) 30 mg capsules under fasting conditions.

INTRODUCTION:

Nicardipine is a calcium entry blocker which inhibits the transmembrane influx of calcium ions into cardiac muscle and smooth muscle without changing serum calcium concentrations.

It is completely absorbed following oral administration. Plasma levels are detected as early as 20 minutes following an oral dose and maximum plasma levels are observed within 30 minutes to 2 hours (mean Tmax = 1 hour). While Cardene is completely absorbed, it is subject to saturable first pass metabolism and the systemic bioavailability is about 35% following a 30 mg oral dose at steady state. Food affects the rate and extent of absorption.

Following oral administration, increasing doses results in a disproportionate increase in plasma levels. Steady state Cmax values following 20, 30, and 40 mg doses every 8 hours averaged 36, 88, and 133 ng/mL, respectively. A similar disproportionate increase in AUC with dose was observed. Terminal plasma half-life averaged 8.6 hours following 30 and 40 mg doses at steady state. The terminal half-life represents the elimination of less than 5% of the absorbed drug.

IN-VIVO STUDY:

The bioequivalence study was conducted by
under the supervision of and

STUDY DESIGN:

The study was designed as a randomized, single dose, two-way crossover bioequivalence study in 37 healthy volunteers under fasting conditions.

Subjects:

The study employed thirty-seven (37) healthy male volunteers between the ages of 19-55, whose weight did not deviate by more than ±15% of the ideal for their height and age (Metropolitan Life Insurance Company Bulletin,1983). Volunteers without history of serious gastrointestinal, hepatic, cardiovascular, hematological or renal disease were employed. In addition, subjects were required to be without history of alcohol or drug use and prior sensitivity to drug product being tested.

Good health was ascertained from medical history, physical examination and routine laboratory tests (blood chemistry, hematology, urinalysis). The subjects were required not to take any prescription medications and/or OTC preparations for atleast 7 days prior to the start and until the end of the study. The volunteers were not allowed to drink alcoholic beverages or caffeine-containing products for 24 hours prior to dosing until after completion of the study. Each subject will sign a written informed consent.

The subjects will remain in the clinic from 12 hours before the drug administration till the completion of the study.

Methods:

The product and dosage employed in this study were as follows:

A. Test: One 30 mg nicardipine hydrochloride capsule (test drug), lot # ND-156 with 240 mL of water. Batch size: capsules, Expiry Date: 5/95

B. Reference: One 30 mg Cardene capsule (Syntex), lot # 86777 with 240 mL of water. Expiry Date: 4-95.

The subjects fasted from 10 hours before until 5 hours following drug administration. No meals were served within 5 hours of any dose. Water ad lib was allowed except within 1 hour of the drug administration.

15 mL of venous blood were drawn in Vacutainers with heparin at 0, 0.25, 0.5, 0.75, 1, 1.33, 1,67, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, and 18 hours. The plasma was separated and promptly frozen for analysis.

WASHOUT PERIOD: one week

ANALYTICAL METHODOLOGY:

ASSAY VALIDATION:

DATA ANALYSIS:

Statistical significance of differences due to treatments, study days, dosing sequence, subjects within sequence, in plasma nicardipine concentrations at each sampling time and nicardipine pharmacokinetic parameters were determined by analysis of variance (ANOVA) using Statistical Analysis Systems (SAS) general linear model (GLM) procedure. 90% confidence intervals (two one-sided t-test) were calculated for nicardipine pharmacokinetic parameters.

IN VIVO BIOEQUIVALENCE STUDY RESULTS:

Of the thirty-seven (37) subjects, 34 completed the crossover. The plasma samples from 34 subjects were assayed for nicardipine as per the protocol. The results of the study comparing the bioavailability of nicardipine test and reference products are given in Table 1 and 2. The mean plasma nicardipine concentrations for test and reference treatments are given in Figure 1.

TABLE 1

Mean Plasma Concentration of Nicardipine (N= 34)

Time (hours)	Zenith's Nicardipine Lot # ND-156 ng/mL (CV%)	Syntex's Cardene Lot # 86777 ng/mL (CV%)	Ratio T/R
0.00	0.0	0.0	
0.25	0.28 (316)	0.23 (305)	1.26
0.50	18.1 (88)	8.8 (110)	2.06
0.75	28.8 (63)	24.2 (75)	1.19
1.00	30.4 (59)	29.2 (66)	1.04
1.33	26.3 (67)	30.5 (95)	0.86
1.67	19.2 (61)	25.5 (82)	0.75
2.00	14.7 (54)	19.9 (68)	0.74
3.00	7.5 (59)	9.3 (71)	0.81
4.00	4.2 (56)	5.1 (74)	0.82

5.00	2.5 (59)	3.0 (74)	0.83
6.00	1.4 (85)	1.7 (95)	0.82
8.00	0.56 (141)	0.77 (135)	0.73
10.00	0.07 (409)	0.37 (197)	0.18
12.00	0.00 (---)	0.08 (406)	0.00
14.00	0.00 (---)	0.03 (583)	0.00
16.00	0.00 (---)	0.00 (---)	--
18.00	0.00 (---)	0.00 (---)	--

TABLE 2

A Summary of Pharmacokinetic Parameters for 34 Subjects

Parameters	Zenith's Nicardipine (CV%)	Syntex's Cardene (CV%)	% Diff	90% Confidence Interval
AUC_{0-18} ng.hr/mL	61.87 (47)	69.97 (58)	11.58	79; 98
AUC_{inf} ng.hr/mL	64.99 (11)	71.68 (58)	9.33	80; 99
C_{max} ng/mL	37.87 (50)	42.70 (66)	11.31	77; 100
T_{max} hours	0.99 (50)	1.10 (48)	10.00	
K_{el} 1/hr	0.519 (33)	0.517 (35)	0.39	
$t_{1/2}$ hours	1.52 (40)	1.53 (39)	0.65	
Ln AUC_{0-18} ng.hr/mL	4.02 (11)	4.09 (13)		84; 102
Ln AUC_{inf} ng.hr/mL	4.08 (11)	4.13 (13)		85; 104
Ln C_{max} ng/mL	3.54 (12)	3.59 (16)		86; 105

The nicardipine AUC_{0-18} and AUC_{inf} produced by Zeneth. formulation are 11.58% and 9.33% lower than the respective values for the reference drug. The C_{max} is 11.31% lower than the reference. The K_{el} and $t_{1/2}$ values differ by 0.39% and 0.65% respectively. The firm did calculate Ln AUC and Ln Cmax for nicardipine and the 90% confidence intervals for log-transformed parameters were 84 to

102 for Ln AUCo-t, 85 to 104 for Ln AUCinf and 86 to 105 for Ln Cmax.

The 90% confidence intervals for untransformed nicardipine AUCo-t was 79 to 98; for AUCinf was 80 to 99 and for C_{max} was 77 to 100. The 90% confidence intervals for AUC0-t and Cmax were outside the range of ±20% limits. The firm did calculate Ln AUC and Ln Cmax for nicardipine and the 90% confidence intevals for log-transformed parameters were 84 to 102 for Ln AUCo-t, 85 to 104 for Ln AUCinf and 86 to 105 for Ln Cmax. These results showed that the two products are bioequivalent. The nicardipine concentration/time profiles of the two products were virtually superimposable with less than 20% difference between the products being observed at each of the timed collection points except at 0.5, 1.67, 2, and 10 hours.

Three subjects were withdrawn from the study. Subject # 1, was dropped during phase 1 due to adverse reaction. subject # 30 was withdrawn during phase 1 because he refused to comply with the study schedule and exhibited disruptive behavior and subject # 36 failed to return to complete the phase 2.

Fifteen subjects reported adverse experience during the study (Table 3). Subject # 1 was withdrawn from the study after 1.33 hours blood sample collection, phase 1, due to complaints of chills, tightness in chest and shortness of breath. The subject was transported to local hospital for evaluation. The subject exited the emergency room against medical advice.

On the basis of fasting in vivo bioavailability data it is determined that Zenith's nicardipine capsules, 30 mg and Syntex's Cardene capsules, 30 mg are bioequivalent.

DISSOLUTION TEST RESULTS:

In vitro dissolution testing was conducted in 900 mL of 0.1N HCl at 37°C using USP XXII apparatus 1 (Basket) at 100 rpm. Results are presented in Table 5. Both the test and reference products meet the dissolution specifications of not less than of the labeled amount of the drug dissolved from the tablet in 30 minutes. This is the method used by the sponsor. This method is not acceptable to the Division of Bioequivalence. The sponsor should conduct the dissolution as described in comment # 4.

The batch size was capsules.

The lots of test and reference products employed in the in vitro dissolution test were identical to those employed in the in vivo bioequivalence study.

COMMENTS:

1. The study was conducted in 34 healthy volunteers and data was assayed as per the protocol, comparing the plasma concentrations from Zenith's nicardipine 30 mg capsule to that of reference , 30 mg Cardene capsule manufactured by Syntex.

The nicardipine AUC_{0-18}, AUC_{inf}, and C_{max} of Zenith's formulation were 11.58% lower, 9.33% lower and 11.31% lower respectively than the corresponding Syntex's reference values. The differences were not statistically significant for AUCinf and Cmax but statistically significant for AUC0-t. The 90% confidence intervals for AUC0-18 and Cmax were outside the limit of ±20% but log-transformed Ln AUCo-t, Ln AUCinf and Ln Cmax were within the limits of 80 to 125 as required by the Division of Bioequivalence for defining products bioequivalence. Therefore, the test drug is bioequivalent to the reference product under fasting conditions. Both treatments yielded similar mean plasma nicardipine concentration-time profiles.

2. Analysis of variance indicated no statistically significant treatment or sequence differences for AUC and C_{max}.

3. Sitting blood pressure and heart rate measurements were monitored at approximately 1, 2, 3, 4, 6, 12, and 24 hours after drug administration. Based on the arithmetic means, systolic blood pressure was significantly decreased from 2 to 4 hours after the test formulation and at 4 hours after the reference formulation. The maximum effect was a decrease of 7.0 mmHg at 2 hours after the Zenith dose and a decrease of 6.8 mmHg at 4 hours after the Syntex dose (Figure 2 and 3).

The mean diastolic blood pressure was significantly decreased from 1 to 12 hours after the test formulation and from 1 to 4 hours after the reference formulation (Figure 4 and 5).

The mean change in pulse rate revealed a statistically significant increase at 1, 2, 6, 12 and 24 hours after the test formulation and 2, 6, 12, and 24 hours after the reference formulation (Figure 6 and 7).

4. The <u>in vitro</u> dissolution testing conducted by the sponsor on both the test and reference products are not acceptable to the Division of Bioequivalence. The sponsor should conduct dissolution testing in 900 mL of 0.333 M Citrate Buffer, pH 4.5 at 37°C using USP XXII apparatus 2 (Paddle) at 50 rpm. The test drug and reference products should show greater than of the labeled amount of nicardipine HCl dissolved in 30 minutes.

5. The lots of test and reference products employed in the <u>in vitro</u> dissolution test were identical to those employed in the <u>in vivo</u> bioequivalence study.

6. The in vivo fasting bioequivalence study and in vitro dissolution testing are not acceptable.

DEFICIENCY: 1. The sponsor should follow the FDA dissolution specification. The sponsor should conduct the dissolution testing in 900 mL of 0.333 M Citrate Buffer, pH 4.5 at 37°C using USP XXII apparatus 2 (Paddle) at 50 rpm. The test product shows greater than of the labeled amount of nicardipine HCl dissolved in 30 minutes.

RECOMMENDATIONS:

1. The application is incomplete and the study will not be accepted until the sponsor completes a sucessful dissolution testing as described below.

2. The in vitro test results are not acceptable. The dissolution testing should be conducted in 900 mL of 0.333M Citrate buffer, pH 4.5 at 37°C using USP XXII apparatus 2 (paddle) at 50 rpm. The test should meet the following specifications:

> Not less than of the labeled amount of the drug in the capsule is dissolved in 30 minutes.

3. The fasting bioequivalence study conducted by Zenith Laboratories on its Nicardipine Hydrochloride capsules, lot # ND-156, comparing it to Cardene capsules, lot # 86777 manufactured by Syntex show that two products are bioequivalent.

4. The waiver of in vivo bioequivalence study for 20 mg Nicardipine Hydrochloride capsule will not be granted at this time. It will be granted upon successful completion of dissolution on all strengths. The firm should resubmit the waiver request.

The firm should be informed of the recommendations.

TABLE 4

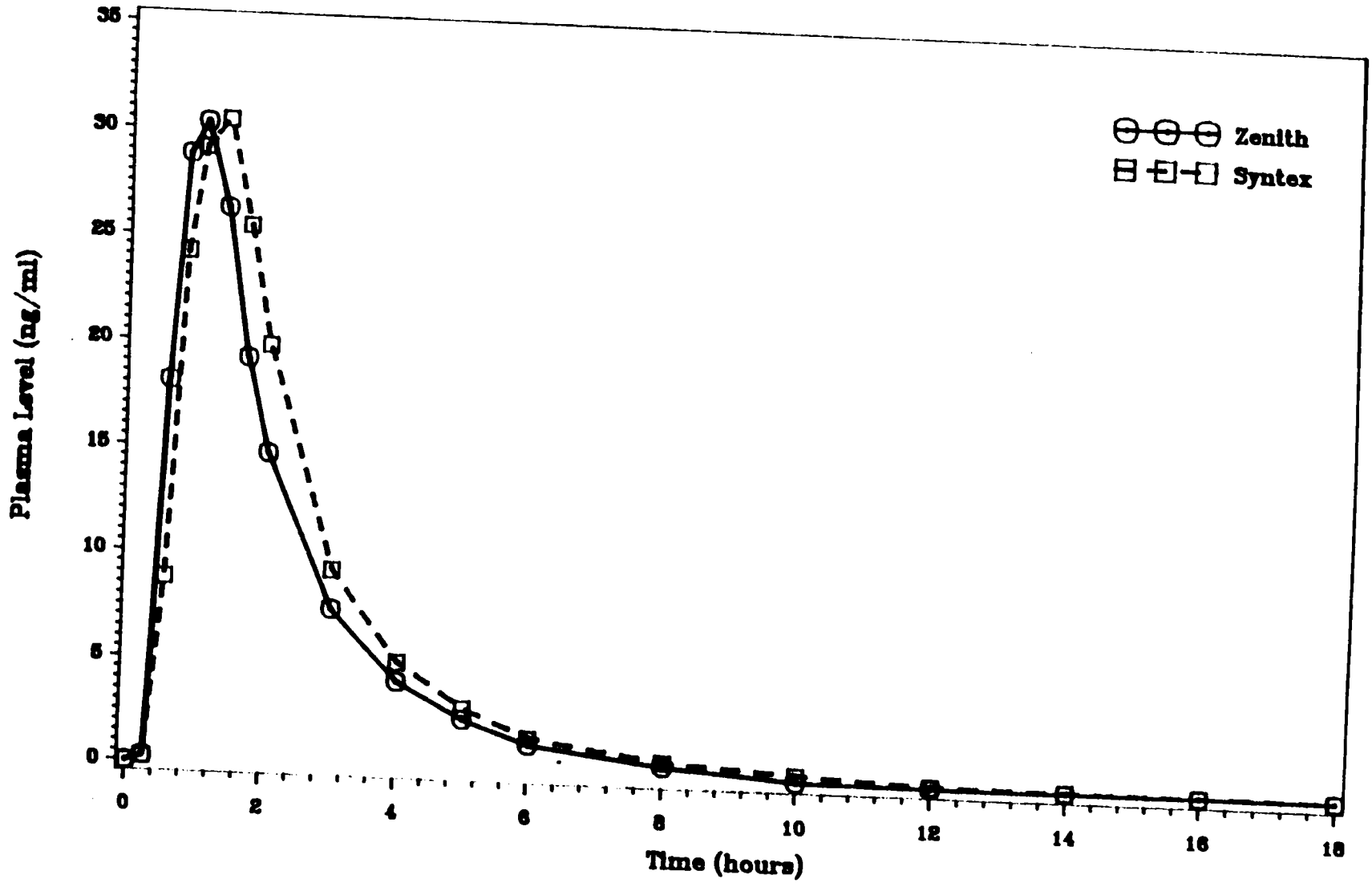
FORMULATIONS

INGREDIENTS	**30 mg Capsule**	**20 mg Capsule**
Nicardipine HCl Pregelatinized Starch, NF Magnesium Stearate, NF	30.00 mg	20.00 mg
Total	240.00 mg	160.00 mg

FIGURE 1

Mean Nicardipine Plasma Levels

n = 34



Drug (Generic Name): NICARDIPINE HCl Firm: Zenith

Dose Strength: 30 mg

ANDA # 74-439 Submission Date: 12/21/93

Table 5- In-Vitro Dissolution Testing

I. Conditions for Dissolution Testing:

USP XXI Basket ✓ Paddle ___ RPM 100 No. Units Tested: 12

Medium: 0.1N HCl at 37°C Volume: 900 ml

Reference Drug: (Manuf.) Syntex

Assay Methodology: _____

II. Results of In-Vitro Dissolution Testing:

Sampling Times (Min.) ~~(Hr.)~~	Test Product Mean % Dissolved	Range	~~(CV)~~ RSD	Reference Product Mean % Dissolved	Range	~~(CV)~~ RSD
	Lot # ND-156			Lot # 86777		
	Strength (mg) 30			Strength (mg) 30		
10	~~85~~ 93.4		(5.1)	95.2		(2.3)
20	97.9		(4.2)	97.7		(1.2)
30	98.7		(4.0)	98.0		(1.0)
45	99.3		(3.9)	98.4		(1.3)
60	100.5		(4.7)	98.7		(1.2)
	Lot # _____			Lot # 20		
	Strength (mg) 20 mg			Strength (mg) 20 mg		
10	96.8		(0.7)	95.6		(1.4)
20	99.0		(0.7)	99.5		(1.5)
30	100.3		(0.8)	99.9		(1.5)
45	100.9		(0.8)	99.7		(1.9)
60	101.1		(0.7)	100.2		(1.7)

Specification:

TABLE 3: POSTSTUDY LABORATORY ABNORMALITIES
NICARDIPINE HYDROCHLORIDE CAPSULES

SUBJECT	TEST	PRESTUDY DATE	RESULT	POSTSTUDY DATE	RESULT	REPEAT DATE	RESULT	NORMAL RANGE
2	CHOLESTEROL	09/14/93	*277	09/25/93	285	--	--	High - over 239
	TRIGLYCERIDE		Not Performed		817	--	--	20 - 200 MG/DL
6	HEMOGLOBIN	09/09/93	*12.9	09/25/93	12.3	--	--	13.5 - 17.5 GM/DL
10	URINALYSIS							
	BLOOD	09/10/93	Negative	09/25/93	Trace	--	--	Negative
12	URINALYSIS							
	LEUKOCYTE ESTERASE	08/23/93	Negative	09/25/93	Positive	--	--	Negative
	WBC/HPF		0		10 - 15	--	--	0 - 5
21	HEMOGLOBIN	09/14/93	13.8	09/25/93	12.1	--	--	13.5 - 17.5 GM/DL
27	RED BLOOD CELL COUNT	09/14/93	4.66	09/25/93	3.34	**10/01/93	4.01	4.4 - 6.0 M/CMM
	HEMOGLOBIN		13.7		10.0		12.3	13.5 - 17.5 GM/DL
	HEMATOCRIT		42.9		31.2		37.3	40 - 53 %
37	HEMOGLOBIN	07/26/93	*12.8	09/25/93	12.3	--	--	13.5 - 17.5 GM/DL

* = Not Clinically Significant.

** = Subject #27 repeated on 10/18/93 results were; RBC *4.33, Hemoglobin *12.8, and Hematocrit 40.2.

FIGURE 2

NICARDIPINE

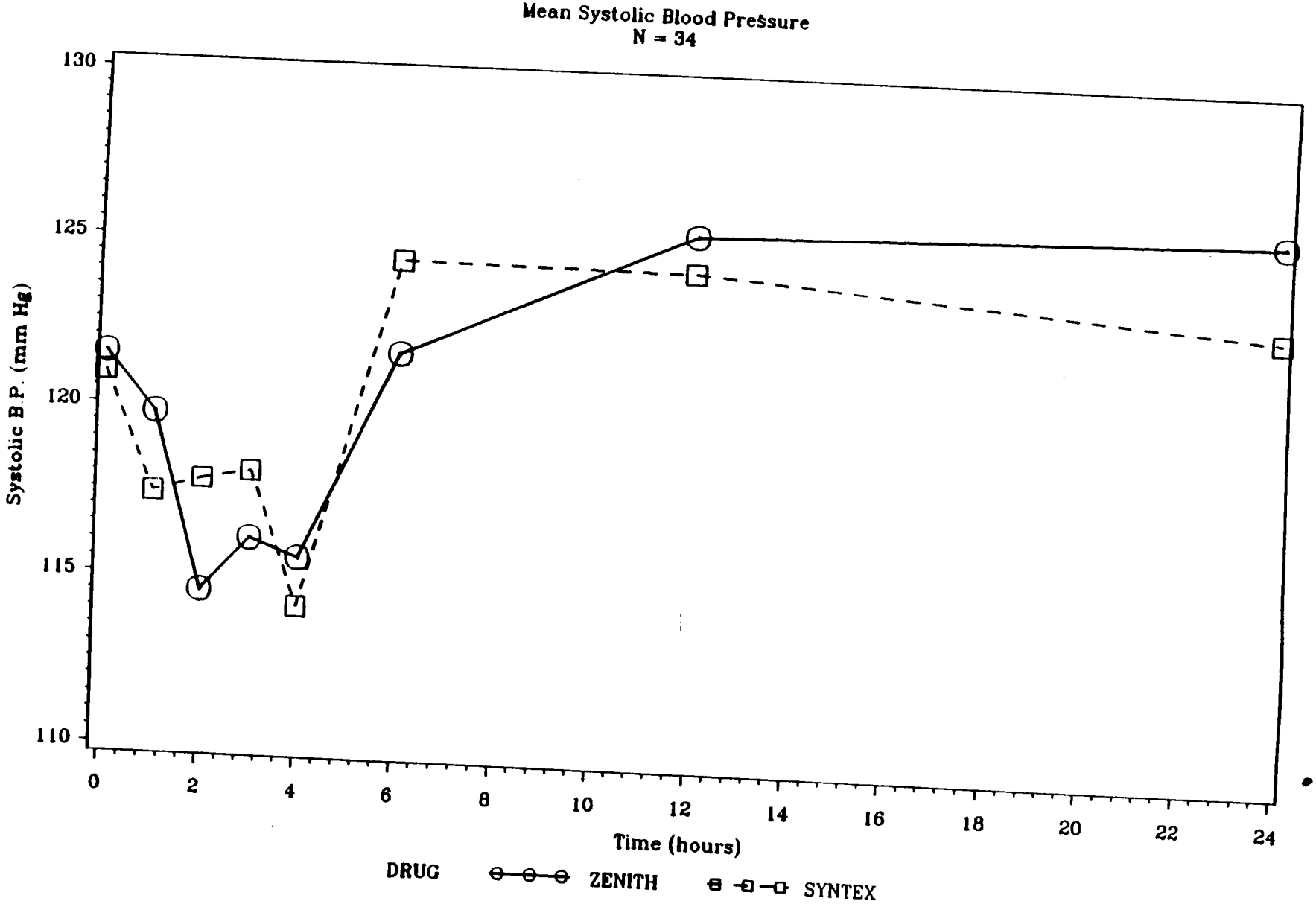


FIGURE 3

NICARDIPINE

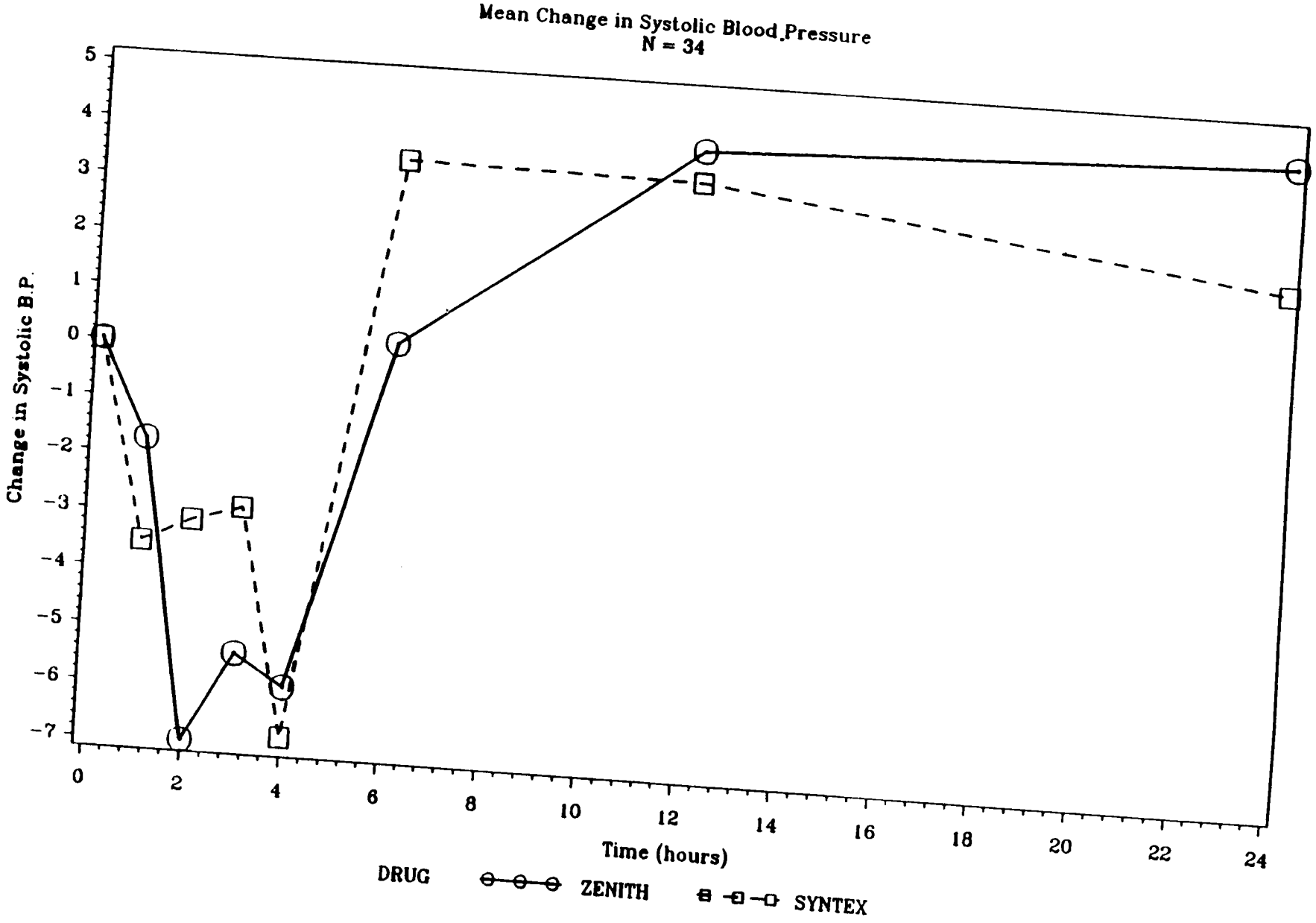


FIGURE 4

NICARDIPINE

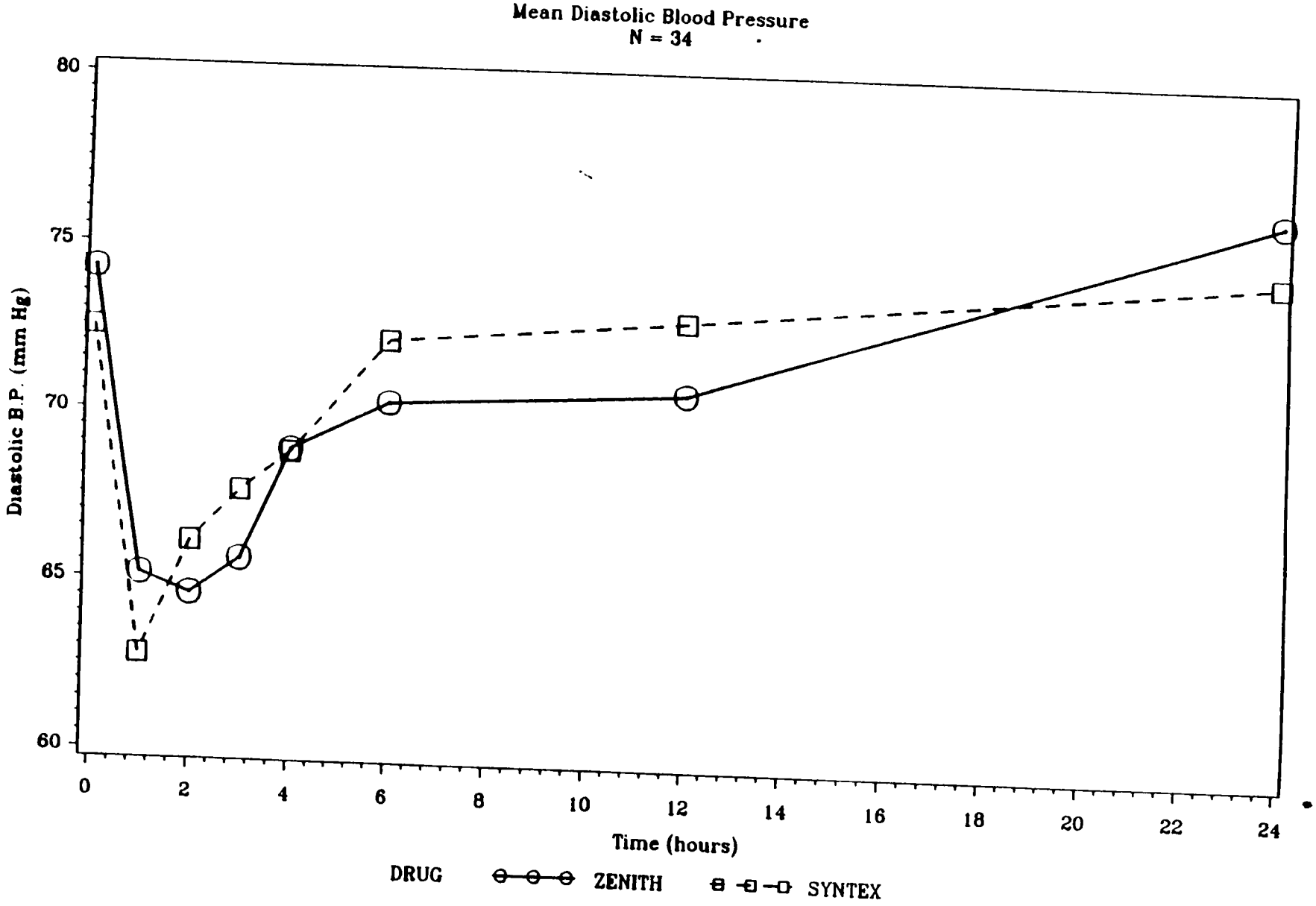


FIGURE 5

NICARDIPINE

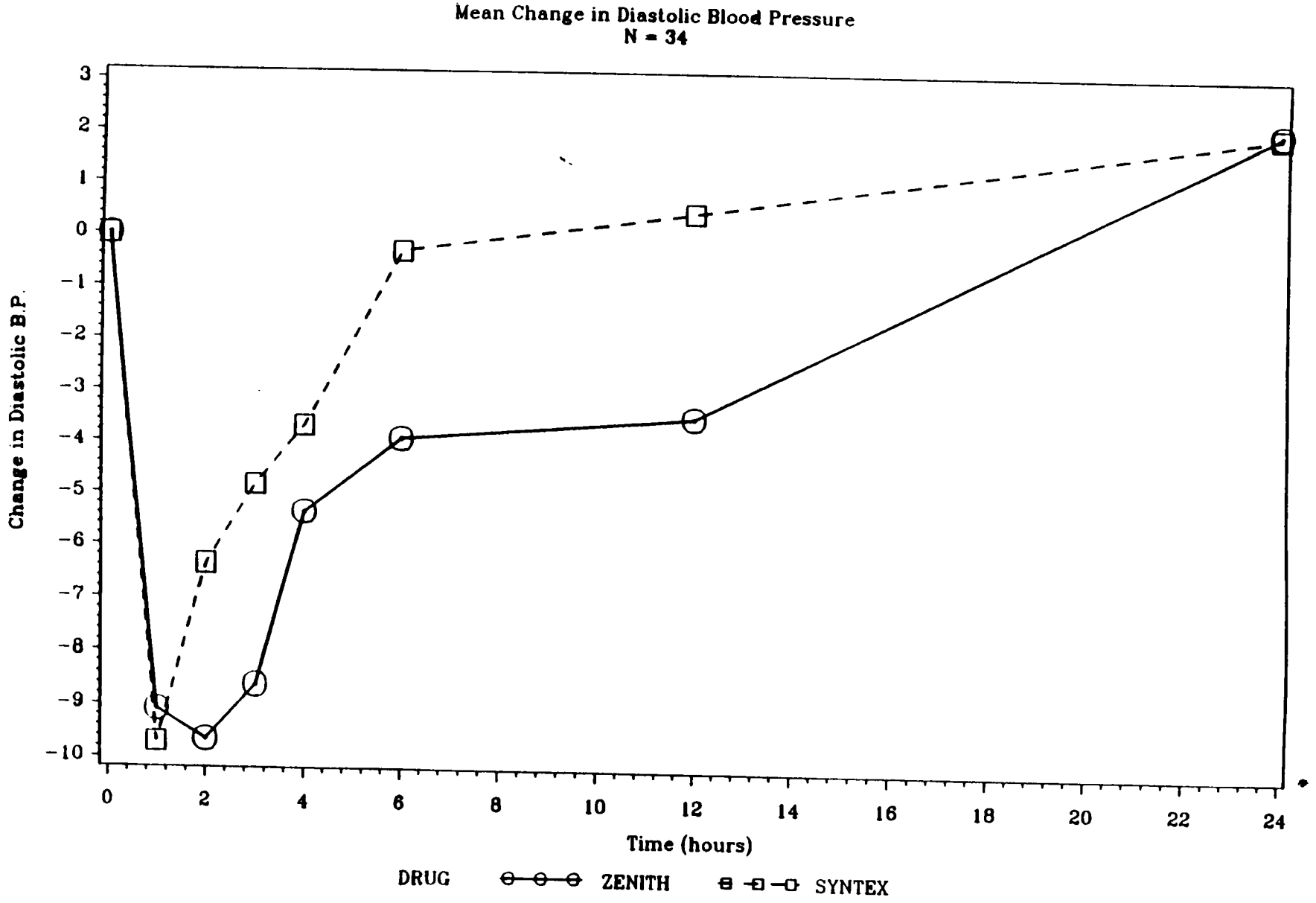


FIGURE 6

NICARDIPINE

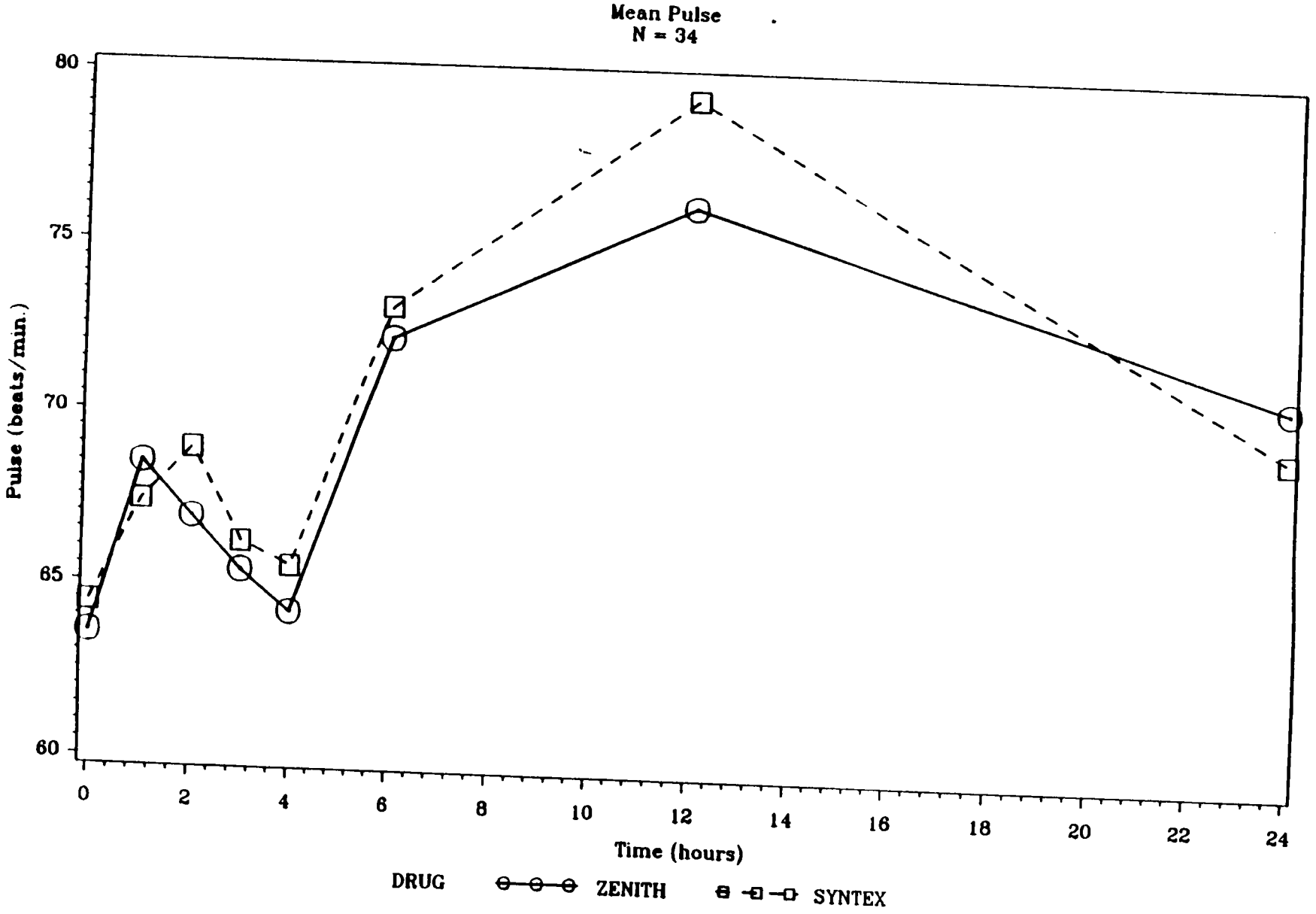
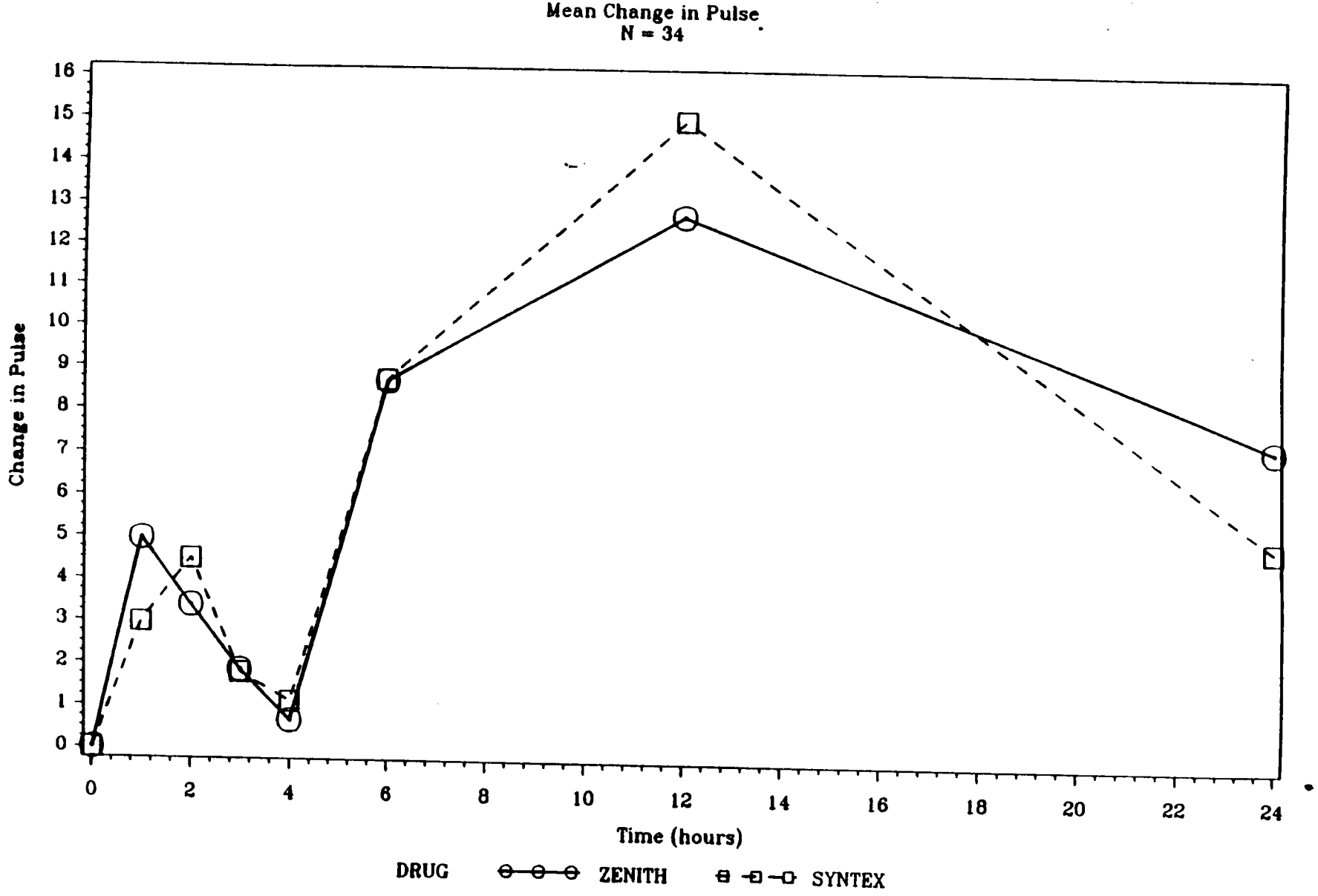


FIGURE 7

NICARDIPINE



MAY 10 1995

Nicardipine Hydrochloride
20 mg and 30 mg Capsules
ANDA # 74-439
Reviewer: Man M. Kochhar

Zenith Laboratories, Inc.
Northvale, New Jersey
Submission Date:
November 15, 1994

REVIEW OF DISSOLUTION DATA AND A WAIVER REQUEST

The firm with an acceptable bioequivalence study has submitted dissolution data for 20 mg and 30 mg capsules. At the time of original submission the application was incomplete because of unacceptable dissolution.

DISSOLUTION TEST RESULTS:

In vitro dissolution testing was conducted in 900 mL of pH 4.5 Citrate Buffer (0.0333M) at 37° C using USP XXII apparatus 2 (paddle) at 50 rpm. Results are presented in Table 1. Both the test and reference products meet the dissolution specifications of not less than of the labeled amount of drug dissolved from the capsules in 30 minutes.

COMMENTS:

1. The firm has submitted an acceptable bioequivalence study under fasting and non-fasting conditions. The in vitro dissolution test results are acceptable.

2. The firm has demonstrated that the formulation of its nicardipine hydrochloride capsules 20 mg and 30 mg are proportional with respect to active and inactive ingredients, Table 2.

3. The waiver of in vivo bioequivalence study requirement for 20 mg capsule should be granted based on 21 CFR 320.22 (d)(2).

DEFICIENCY: None

RECOMMENDATIONS:

1. The dissolution testing conducted by Zenith Laboratories on its Nicardipine Hydrochloride 30 mg and 20 mg capsules is acceptable. The firm has previously conducted an acceptable fasting and non-fasting bioequivalence study on its 30 mg capsules. Therefore, the waiver of in vivo bioequivalence study requirement for Zenith Laboratories 20 mg capsule is granted. The 20 mg Nicardipine Hydrochloride capsules from Zenith Laboratories are, therefore, deemed bioequivalent to 20 mg capsules of Cardene manufactured by Syntex based on 21 CFR 320.22 (d)(2).

2. The dissolution testing should be incorporated into the firm's manufacturing controls and stability programs. The dissolution

testing should be conducted in 900 mL of 0.0333M Citrate Buffer, pH 4.5 at 37° C using USP XXII apparatus 2 (paddle) at 50 rpm. The test should meet the following specifications:

> Not less than of the labeled amount of the drug in the capsule is dissolved in 30 minutes.

The firm should be informed of the recommendations.

Man M. Kochhar, Ph.D.
Review Branch III
Division of Bioequivalence

RD RMHATRE
FT RMHATRE _____ 5/9/95

Concur: _____ Date: 5/10/95
Keith K. Chan, Ph.D.
Director
Division of Bioequivalence

MMKochhar/mmk/4-21-95; 5-5-95

cc: ANDA # 74-439 (Original, Duplicate), HFD-600 (Hare), HFD-630, HFD-658 (Mhatre, Kochhar), Drug File, Division File

(Please select Typeover for Input.)

Table 1. In Vitro Dissolution Testing

Drug (Generic Name):Nicardipine HCl Capsules
Dose Strength:30 mg, Lot # ND-156
ANDA No.:74-439
Firm:Zenith Laboratories
Submission Date:9/15/94
File Name:

I. Conditions for Dissolution Testing:

USP XXII Basket: Paddle:x RPM: 50
No. Units Tested: 12
Medium:0.0333M Citrate Buffer, pH 4.5 Volume: 900 mL
Specifications:NLT in 30 Min
Reference Drug: Syntex's Cardine Capsule. Lot #86777
Assay Methodology:

II. Results of In Vitro Dissolution Testing:

Sampling Times Minutes	Test Product Lot # ND-156 Strength(30 mg)			Reference Product Lot # 86777 Strength(30 mg)		
	Mean %	Range	%RSD	Mean %	Range	%RSD
10	85		9.3	78		12.3%
20	92		8.5	97		6.0
30	94		7.2	98		4.6
45	95		5.7	99		3.7
60	97		4.8	100		3.1

Sampling Times Minutes	Test Product Lot # ND-168 Strength(20mg)			Reference Product Lot # 76710 Strength(20mg)		
	Mean %	Range	%RSD	Mean %	Range	%RSD
10	93		3.9	89		7.7
20	97		3.1	97		4.3
35	97		3.0	97		3.7
45	98		3.3	98		3.0
60	99		2.9	98		2.8

TABLE 2

FORMULATION

INGREDIENTS	30 mg Capsule	20 mg Capsule
Nicardipine Hydrochloride	30.00 mg	20.00 mg
Pregelatinized Starch, NF		
Magnesium Stearate, NF		
TOTAL	240.00 mg	160.00 mg

APR 23 1994

Nicardipine Hydrochloride
Capsules, 20 mg and 30 mg
ANDA # 74-439
Reviewer: Man M. Kochhar
74439.SDW.294

Zenith Laboratories Inc.
Northvale, N.J.
Submission Date:
February 10, 1994

Review of Bioequivalence Study, Waiver Request and Dissolution (NON-FASTING)

OBJECTIVE:

The objective of this study was to compare the bioavailability of two formulations of nicardipine hydrochloride, 30 mg capsules of test and reference products under non-fasting conditions. A secondary objective was to compare the Zenith product under fasting and non-fasting conditions.

INTRODUCTION:

Nicardipine is a calcium entry blocker which inhibits the transmembrane influx of calcium ions into cardiac muscle and smooth muscle without changing serum calcium concentrations.

It is completely absorbed following oral administration. Plasma levels are detected as early as 20 minutes following an oral dose and maximum plasma levels are observed within 30 minutes to 2 hours (mean Tmax = 1 hour). While Cardene is completely absorbed, it is subject to saturable first pass metabolism and the systemic bioavailability is about 35% following a 30 mg oral dose at steady state. Food affects the rate and extent of absorption.

Following oral administration, increasing doses results in a disproportionate increase in plasma levels. Steady state Cmax values following 20, 30, and 40 mg doses every 8 hours averaged 36, 88, and 133 ng/mL, respectively. A similar disproportionate increase in AUC with dose was observed. Terminal plasma half-life averaged 8.6 hours following 30 and 40 mg doses at steady state. The terminal half-life represents the elimination of less than 5% of the absorbed drug.

IN-VIVO STUDY:

The objective of this study was to compare the bioavailability of Zenith Laboratories and Syntex (Cardene) 30 mg capsules under non-fasting conditions. A secondary objective was to see the effect of Zenith product under fasting and non-fasting conditions.

The bioequivalence study was conducted by
under the supervision of and

STUDY DESIGN:

1. The study was designed as a randomized, single dose, two-way crossover bioequivalence study in 18 healthy volunteers under non-fasting conditions.

2. To compare the plasma levels of Zenith's nicardipine under fasting and non-fasting conditions.

Subjects:

The study employed eighteen (18) healthy male volunteers between the ages of 19-55, whose weight did not deviate by more than ±15% of the ideal for their height and age (Metropolitan Life Insurance Company Bulletin,1983). Volunteers without history of serious gastrointestinal, hepatic, cardiovascular, hematological or renal disease were employed. In addition, subjects were required to be without history of alcohol or drug use and prior sensitivity to drug product being tested.

Good health was ascertained from medical history, physical examination and routine laboratory tests (blood chemistry, hematology, urinalysis). The subjects were required not to take any prescription medications and/or OTC preparations for atleast 7 days prior to the start and until the end of the study. The volunteers were not allowed to drink alcoholic beverages or caffeine-containing products for 24 hours prior to dosing until after completion of the study. Each subject will sign a written informed consent.

The subjects will remain in the clinic from 12 hours before the drug administration till the completion of the study.

Methods:

The product and dosage employed in this study were as follows:

Treatment A. Test:	One 30 mg nicardipine hydrochloride capsule (test drug), lot # ND-156 with 240 mL of water following a standard meal (non-fasting). Batch size: capsules, Expiry Date: 5/95
Treatment B. Reference:	One 30 mg Cardene capsule (Syntex), lot # 86777 with 240 mL of water following a standard meal (Non-fasting). Expiry Date: 4-95.
Treatment C. Test:	One 30 mg nicardipine hydrochloride capsule (test drug), lot # ND-156 with 240 mL of water (fasting).

The drug products were administered with 240 mL of water. The subjects receiving treatment A and B were served a standard breakfast 35 minutes prior to drug administration. Subjects receiving treatment C, fasted from 10 hours before until 5 hours following drug administration. No meals were served within 5 hours of any dose. Water ad lib was allowed except within 1 hour of the drug administration.

10 mL of venous blood were drawn in Vacutainers with heparin at 0, 0.25, 0.5, 0.75, 1, 1.33, 1,67, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, and 18 hours. The plasma was separated and promptly frozen for analysis.

WASHOUT PERIOD: one week

ANALYTICAL METHODOLOGY:

DATA ANALYSIS:

Statistical significance of differences due to treatments, study days, dosing sequence, subjects within sequence, in plasma nicardipine concentrations at each sampling time and nicardipine pharmacokinetic parameters were determined by analysis of variance (ANOVA) using Statistical Analysis Systems (SAS) general linear model (GLM) procedure.

IN VIVO BIOEQUIVALENCE STUDY RESULTS:

Of the eighteen (18) subjects, 17 completed the crossover. One subject # 11 failed to return to facility to complete phase III.The plasma samples from 17 subjects were assayed for nicardipine as per the protocol. The results of the study comparing the bioavailability of nicardipine test and reference products are given in Table 1 and 2. The mean plasma nicardipine concentrations for test and reference treatments are given in Figure 1.

TABLE 1

Mean Plasma Concentration of Nicardipine (N= 17)

Time (hours)	Zenith's Nicardipine Lot # ND-156 ng/mL (CV%)		Syntex's Cardene Lot # 86777 ng/mL (CV%)
	Fasting	Non-fasting	Non-fasting
0.00	0.00 (---)	0.00 (---)	0.00 (---)
0.25	0.21 (311)	0.07 (412)	0.00 (---)
0.50	18.01 (100)	0.31 (412)	0.22 (412)
0.75	32.83 (84)	1.08 (208)	0.51 (341)
1.00	30.54 (71)	2.76 (132)	1.35 (251)
1.33	22.83 (60)	4.92 (88)	3.07 (152)
1.67	18.49 (65)	7.18 (63)	5.28 (111)
2.00	14.17 (73)	9.86 (54)	7.28 (85)
3.00	7.60 (85)	10.97 (55)	11.60 (70)
4.00	4.13 (73)	6.85 (70)	9.25 (86)
5.00	2.67 (84)	3.46 (80)	4.57 (84)
6.00	1.14 (129)	1.68 (82)	1.90 (92)
8.00	0.53 (165)	0.47 (147)	0.48 (169)
10.00	0.21 (303)	0.09 (412)	0.11 (412)
12.00	0.09 (412)	0.00 (---)	0.08 (412)
14.00	0.07 (412)	0.00 (---)	0.00 (---)
16.00	0.00 (---)	0.00 (---)	0.00 (---)
18.00	0.00 (---)	0.00 (---)	0.00 (---)

TABLE 2

A Summary of Pharmacokinetic Parameters for 17 Subjects

Parameters	Zenith's Nicardipine (CV%) Nonfasting A	Zenith's Nicardipine (CV%) Fasting C	Syntex's Cardene (CV%) Nonfasting B	A/B	A/C
AUC_{0-18} ng.hr/mL	35.46 (48)	61.87 (71)	36.46 (60)	0.97	0.57
AUC_{inf} ng.hr/mL	38.03 (45)	57.61 (53)	43.01 (49)	0.88	0.66
C_{max} ng/mL	13.76 (33)	39.42 (64)	15.34 (56)	0.89	0.35
T_{max} hours	2.33 (31)	0.90 (37)	2.84 (29)	0.82	2.59
K_{el}	0.594 (22)	0.472 (35)	0.642 (23)	0.92	1.26

1/hr					
$t_{1/2}$ hours	1.22 (22)	0.91 (37)	1.19 (47)	1.02	1.34
Ln AUC_{0-18} ng.hr/mL	3.44 (16)	3.92 (16)	3.39 (22)		
Ln AUC_{inf} ng.hr/mL	3.54 (14)	3.92 (13)	3.66 (12)		
Ln C_{max} ng/mL	2.55 (16)	3.46 (20)	2.57 (24)		

The nicardipine AUC_{0-18} and AUC_{inf} produced by Zenith. formulation are 2.74% and 11.58% lower than the respective values for the reference drug. The C_{max} is 10.30% lower than the reference. The Tmax is 17.96% lower than the corresponding reference value. The K_{el} and $t_{1/2}$ values differ by 7.48% and 2.52% respectively. The firm did calculate Ln AUC and Ln Cmax for nicardipine and they are within the range acceptable to the Division of Bioequivalence.

The nicardipine concentration/time profiles of the two products were virtually superimposable with less than 20% difference between the products being observed at each of the timed collection points except at 0.25, and 0.75 hours.

Subject # 11 failed to return to facility to complete phase III. Seventeen subjects completed the study.Several of the subjects experienced adverse reaction during the study (Table 3).

Non-fasting-fasting Comparison (Treatment A vs C) Zenith

The results for untransformed parameters showed decreases of 43% for AUC0-18, 34% for AUCinf, and 65% for Cmax after the meal and Tmax 159% higher after the meal. This showed that food affects the rate and extent of absorption.

Non-fasting Comparison (Treatment A vs B) Zenith vs Syntex

The ratios (A/B) for the untransformed parameters AUC0-t, AUCinf, and Cmax were 0.97, 0.88, and 0.89 respectively. Mean Tmax values were 2.33 and 2.84 hours for Zenith (A) and Syntex (B) products, respectively.

On the basis of non-fasting in vivo bioavailability data it is determined that Zenith's nicardipine capsules and Syntex's Cardene capsules, 30 mg are bioequivalent.

DISSOLUTION TEST RESULTS:

In vitro dissolution testing was conducted in 900 mL of 0.1N HCl at 37°C using USP XXII apparatus 1 (Basket) at 100 rpm. Results are presented in Table 4. Both the test and reference products meet the dissolution specifications of not less than of the labeled amount of the drug dissolved from the capsule in 30 minutes. This dissolution method is unacceptable to the Division of Bioequivalence. The sponsor should follow the dissolution method described in comment # 5.

The batch size was capsules.

The lots of test and reference products employed in the in vitro dissolution test were identical to those employed in the in vivo bioequivalence study.

COMMENTS:

1. The study was conducted in 17 healthy volunteers and data was assayed as per the protocol, comparing the plasma concentrations from Zenith's nicardipine 30 mg capsule to those of reference , 30 mg Cardene capsule manufactured by Syntex. The nicardipine AUC_{0-18}, AUC_{inf}, and C_{max} of Zenith's formulation were 2.74% lower, 11.58% lower and 10.30% lower respectively than the corresponding Syntex's reference values under non-fasting conditions. Several subjects experienced adverse events during the study (Table 3).

2.From 0.5 through 5 hours after dosing, there were significant differences in nicardipine concentrations amongst the three treatments. These significant differences were the result of lower concentrations from 0.5 to 2 hours, and higher concentrations at 3 and 4 hours, when the dose was given following a meal compared to the dose administered after an overnight fast.

3. The analysis of variance indicated no statistically significant treatment or sequence differences for AUC and C_{max}.

4. Sitting blood pressure and heart rate measurements were monitored at approximately 1, 2, 3, 4, 6, 12, and 24 hours after drug administration. Based on the arithmetic means, systolic blood pressure was significantly decreased at 4 hours after the test formulation and at 2, 3, and 4 hours after the reference formulation and Zenith (fasting) dose. The maximum effect was a decrease of 4.1 mmHg at 3 hours after the Zenith dose and a decrease of 6.4 mmHg at 2 hours after the Syntex dose (Figure 2).

The mean diastolic blood pressure was significantly decreased at 4 hours after the test formulation and at 1, 2, 3, 4, and 12 hours after the reference formulation (Figure 3).

The mean change in pulse rate revealed a statistically significant increase from 1 to 24 hours after the test formulation and 1, 12, and 24 hours after the reference formulation (Figure 4).

5. The in vitro dissolution testing conducted on both the test and reference products are not acceptable to the Division of Bioequivalence. The sponsor should conduct dissolution testing in 900 mL of 0.333 M Citrate Buffer, pH 4.5 at 37°C using USP XXII apparatus 2 (Paddle) at 50 rpm. The test drug and reference products should meet the following specifications:

> Not less than of the labeled amount of nicardipine HCl dissolved in 30 minutes.

6. The lots of test and reference products employed in the in vitro dissolution test were identical to those employed in the in vivo bioequivalence study.

7. The in vivo non-fasting bioequivalence study is acceptable.

DEFICIENCY: 1. The firm has used an unacceptable dissolution method. The sponsor should follow the FDA dissolution specification. The sponsor should conduct the dissolution testing in 900 mL of 0.333 M Citrate Buffer, pH 4.5 at 37°C using USP XXII apparatus 2 (Paddle) at 50 rpm. The test product should meet the following specifications:

> Not less than of the labeled amount of nicardipine HCl dissolved in 30 minutes.

RECOMMENDATIONS:

1. This application is incomplete till the sponsor conducts an acceptable dissolution.

2. The non-fasting bioequivalence study conducted by Zenith Laboratories on its Nicardipine Hydrochloride capsules, lot # ND-156, comparing it to Cardene capsules, lot # 86777 manufactured by Syntex has been found acceptable by the Division of Bioequivalence. The firm has conducted an acceptable fasting study under a separate cover.

3. The waiver of in vivo bioequivalence study for 20 mg Nicardipine Hydrochloride capsule will not be granted at this time. The waiver will be granted upon successful completion of in vitro dissolution testing. The firm should resubmit the waiver request with dissolution testing.

4. The firm has used an unacceptable dissolution method and thus the in vitro test results are not acceptable. The dissolution testing should be conducted in 900 mL of 0.333M Citrate buffer, pH 4.5 at 37°C using USP XXII apparatus 2 (paddle) at 50 rpm. The

test should meet the following specifications:

Not less than of the labeled amount of the drug in the capsule is dissolved in 30 minutes.

The firm should be informed of the recommendations.

Man.M.Kochhar, Ph.D
Review Branch III
Division of Bioequivalence

RD INITIALLED MPARK
FT INITIALLED MPARK 4/20/94

Concur: _____ Date: 4/28/94
Ramakant M. Mhatre, Ph.D.
Acting Director
Division of Bioequivalence

MMKochhar/mmk/3-10-94, 4-14-94 74-439 BIO

cc: ANDA # 74-439 original, HFD-230, HFD-604 (Hare), HFD-658 (MPark, Kochhar), Drug File.

Drug (Generic Name): NICARDIPINE HCl Firm: Zenith

Dose Strength: 30 mg

ANDA # 74-439 Submission Date: 12/21/93

Table 4 In-Vitro Dissolution Testing

I. Conditions for Dissolution Testing:

USP XXI Basket ✓ Paddle ___ RPM 100 No. Units Tested: 12

Medium: 0.1N HCl at 37°C Volume: 900 ml

Reference Drug: (Manuf.) Syntex

Assay Methodology:

II. Results of In-Vitro Dissolution Testing:

Sampling Times (Min.)	Test Product Mean % Dissolved	Range	RSD	Reference Product Mean % Dissolved	Range	RSD
	Lot # ND-156			Lot # 86777		
	Strength (mg) 30			Strength (mg) 30		
10	~~93.4~~		(5.1)	95.2		(2.3)
20	97.9		(4.2)	97.7		(1.2)
30	98.7		(4.0)	98.0		(1.0)
45	99.3		(3.9)	78.4		(1.3)
60	100.5		(4.7)	98.7		(1.2)
	Lot # ___			Lot # 20		
	Strength (mg) 20 mg			Strength (mg) 20 mg		
10	96.8		(0.7)	95.6		(1.4)
20	99.0		(0.7)	99.5		(1.5)
30	100.3		(0.8)	99.7		(1.5)
45	100.9		(0.8)	99.7		(1.9)
60	101.1		(0.7)	100.2		(1.7)

Specification:

FIGURE 1

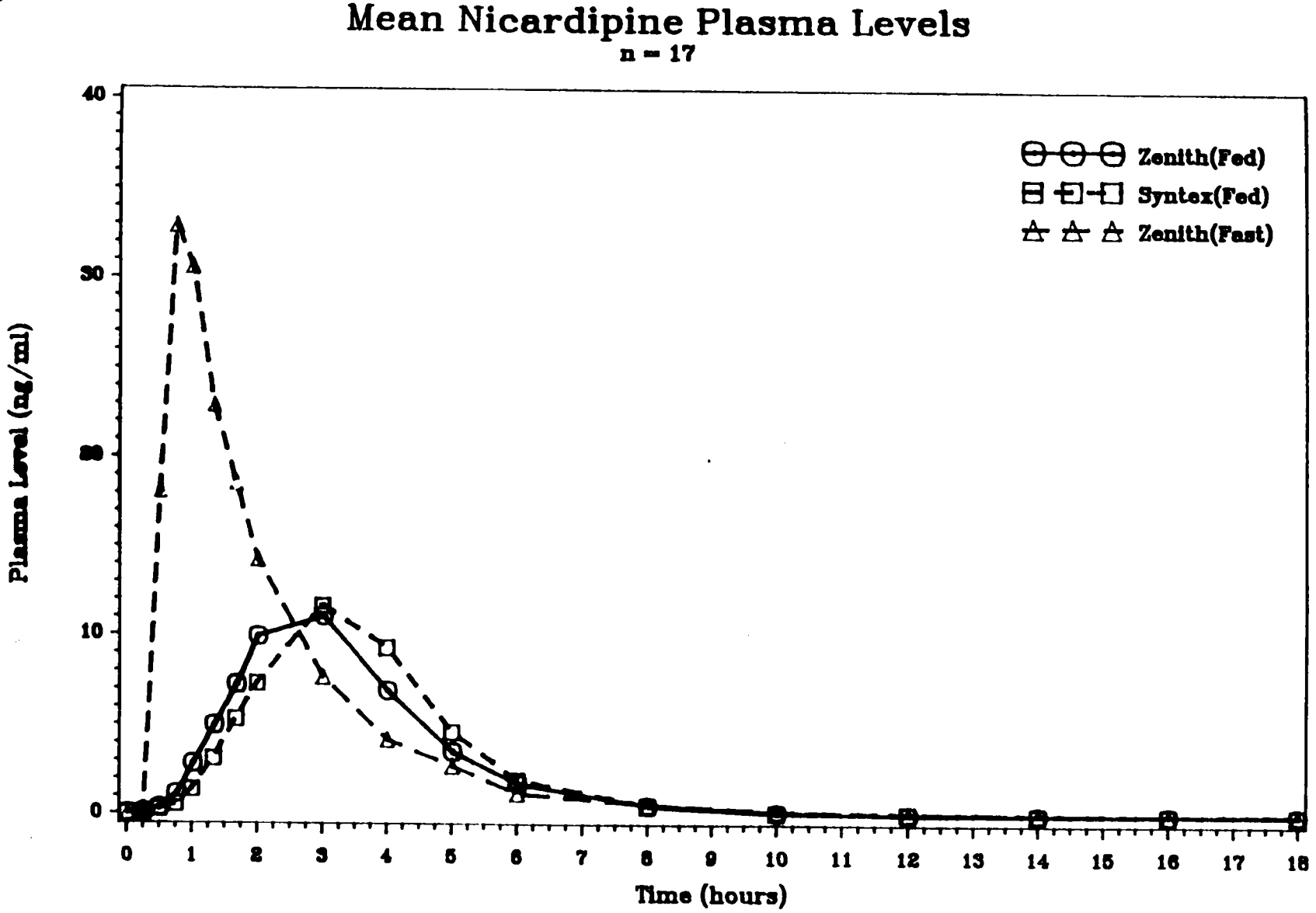

Mean Nicardipine Plasma Levels
n = 17
Zenith(Fed)
Syntex(Fed)
Zenith(Fast)
Plasma Level (ng/ml)
40
30
20
10
0
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18
Time (hours)

TABLE 3: [illegible]

SUBJECT	TEST	PRESTUDY DATE	PRESTUDY RESULT	POSTSTUDY DATE	POSTSTUDY RESULT	REPEAT DATE	REPEAT RESULT	NORMAL RANGE
1	RED BLOOD CELL COUNT	11/23/93	* 4.34	12/30/93	4.17	--	--	4.4 - 6.0 M/CMM
	HEMOGLOBIN		14.0		12.7	--	--	13.5 - 17.5 GM/DL
	HEMATOCRIT		40.7		38.2	--	--	40 - 53 %
2	RED BLOOD CELL COUNT	11/22/93	4.92	12/30/93	4.24	--	--	4.4 - 6.0 M/CMM
	HEMOGLOBIN		15.3		12.4	--	--	13.5 - 17.5 GM/DL
	HEMATOCRIT		45.0		38.1	--	--	40 - 53 %
4	[illegible]	11/29/93	14.2	12/30/93	12.5	--	--	13.5 - 17.5 GM/DL
	MCV		* 78		76	--	--	80 - 100 CUU.
	MCH		* 25.8		23.6	--	--	26 - 33 PG.
	MCHC		33.0		30.9	--	--	31 - 34 %
7	HEMOGLOBIN	11/30/93	* 13.0	12/30/93	11.2	01/13/94	* 12.8	13.5 - 17.5 GM/DL
	HEMATOCRIT		* 39.8		34.5		* 39.3	40 - 53 %
	MCV		* 79		77		* 79	80 - 100 CUU.
	MCH		* 25.9		25.0		* 25.7	26 - 33 PG.
11	GLUCOSE	11/23/93	85	12/30/93	137	--	--	65 - 115 MG/DL
	URINALYSIS							
	BLOOD		Negative		Trace	--	--	Negative
14	RED BLOOD CELL COUNT	12/01/93	4.42	12/30/93	3.98	--	--	4.4 - 6.0 M/CMM
	HEMOGLOBIN		14.1		12.3	--	--	13.5 - 17.5 GM/DL
	HEMATOCRIT		42.3		36.7	--	--	40 - 53 %

* Not Clinically Significant.

TABLE 3: ADVERSE EVENTS
NICARDIPINE HYDROCHLORIDE 30 MG CAPSULES

SUBJECT#	DATE	TIME	EVENT	SEVERITY	RESOLUTION	RELATIONSHIP TO DRUG	Rx	PRODUCT UNDER STUDY
5	12/15/93	0835	Lightheaded	Mild	0850	Possible	None	Syntex
	12/22/93	0855	Drowsy	Mild	1600	Possible	None	Zenith(fed)
6	12/29/93	1000	Sleepy	Mild	1800	Possible	None	Syntex
9	12/15/93	1318	Headache	Mild	1340	Probable	None	Zenith(fed)
10	*12/20/93	~1230	Diarrhea x 5-10	Mild	12/21/93 2200	None	None	Syntex
	*12/20/93	~1230	Stomach pain	Mild	12/21/93 2200	None	None	Syntex
	12/29/93	0818	Stuffy nose	Mild	Unknown	None	None	Zenith(fed)
11	12/22/93	~0900	Intermittent increase pulse	Mild	~2200	Possible	P.O. fluids	Syntex
12	12/15/93	0850	Headache	Mild	1559	Probable	None	Zenith(fasted)
	12/29/93	1145	Headache	Mild	1300	Probable	None	Syntex
13	12/29/93	0800	Sleepy	Mild	1200	None	None	Syntex
15	12/15/93	1300	Headache	Mild	Unresolved at discharge of Phase I	Probable	None	Zenith(fed)
16	**12/25/93	Unknown	Cold symptoms	Mild	Unresolved at discharge of phase III	None	None	Syntex
	12/29/93	0900	Tired	Mild	1200	Possible	None	Zenith(fasted)

* Reported at entry of Phase II, 12/21/93.
** Reported at entry of Phase III, 12/28/93.

TABLE 3: ADVERSE EVENTS
NICARDIPINE HYDROCHLORIDE 30 MG CAPSULES

SUBJECT#	DATE	TIME	EVENT	SEVERITY	RESOLUTION	RELATIONSHIP TO DRUG	Rx	PRODUCT UNDER STUDY
18	12/15/93	1150	Headache	Mild	2100	Probable	None	Zenith(fasted)
	12/16/93	0200	Headache	Moderate	Unresolved at discharge of Phase I	Possible	None	Zenith(fasted)
	*12/21/93	0940	Headache	Mild to Moderate	Unresolved at discharge of Phase II	None	None	Zenith(fasted)
	12/29/93	0930	Headache	Mild	Unresolved at discharge of Phase III	Possible	None	Zenith(fed)

* Reported at entry of Phase II, 12/21/93.
** Reported at entry of Phase III, 12/28/93.

Figure 2
Mean Systolic Blood Pressure
N=17

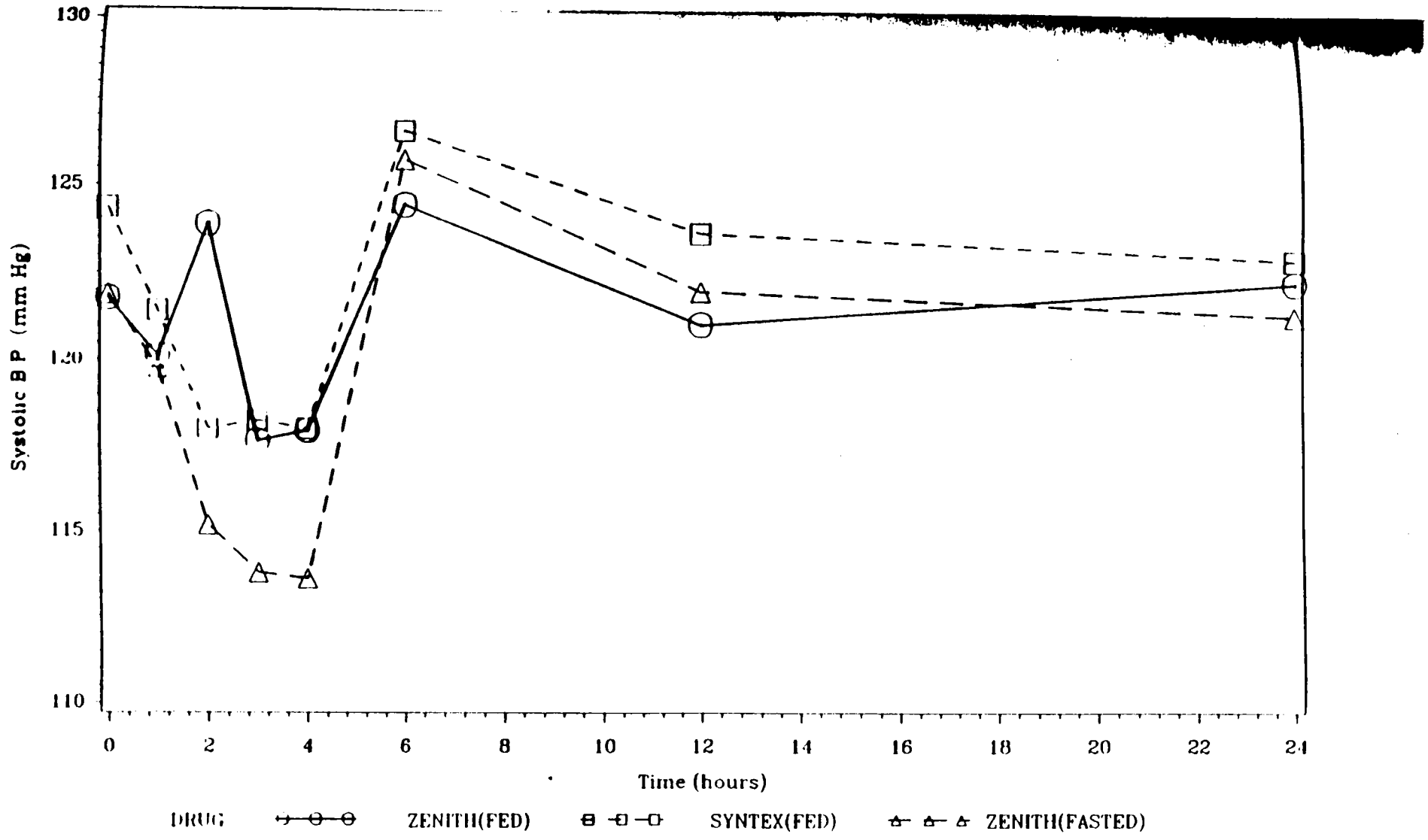


Figure 2
Mean Change in Systolic Blood Pressure
N=17

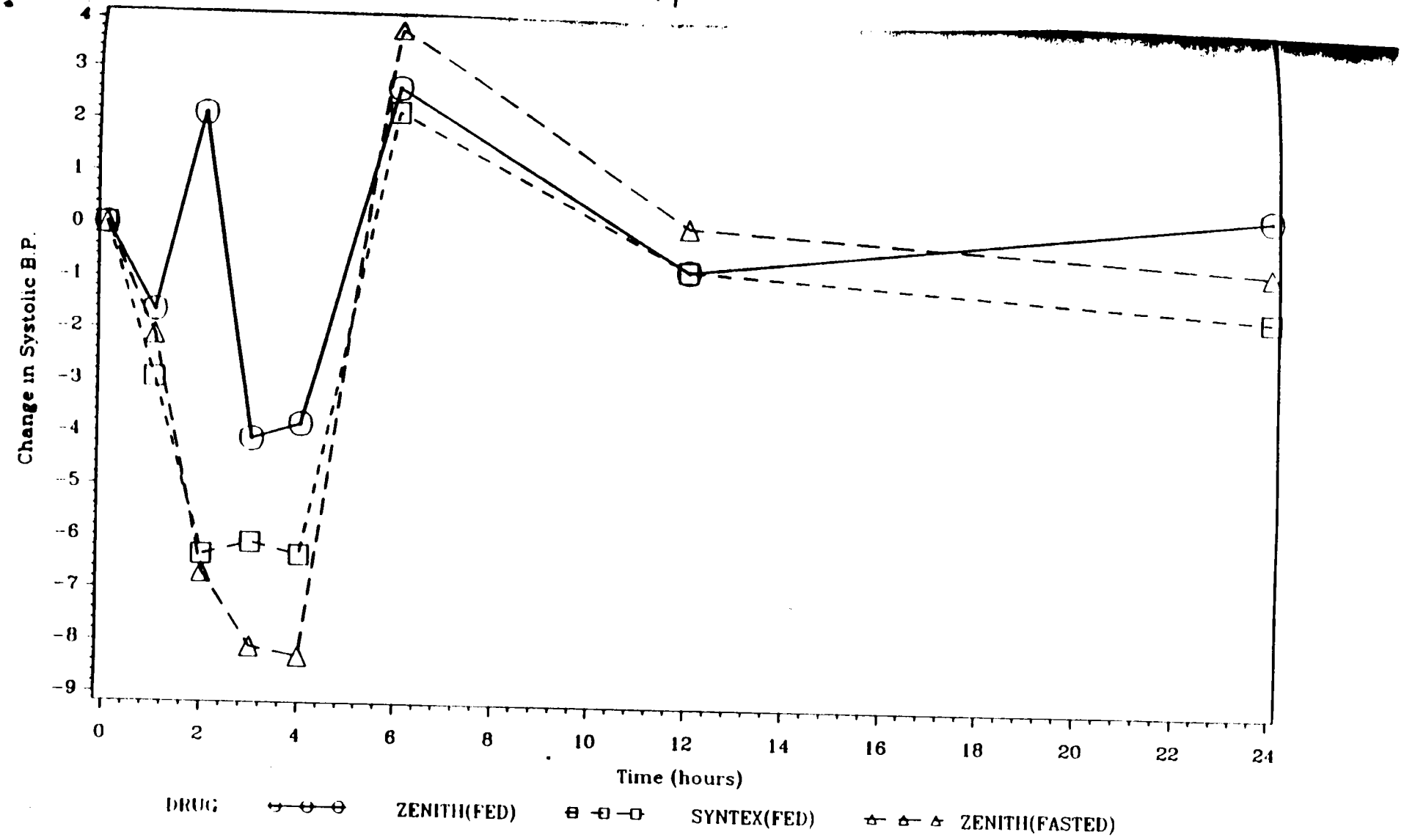


Figure 3

Mean Diastolic Blood Pressure

N = 17

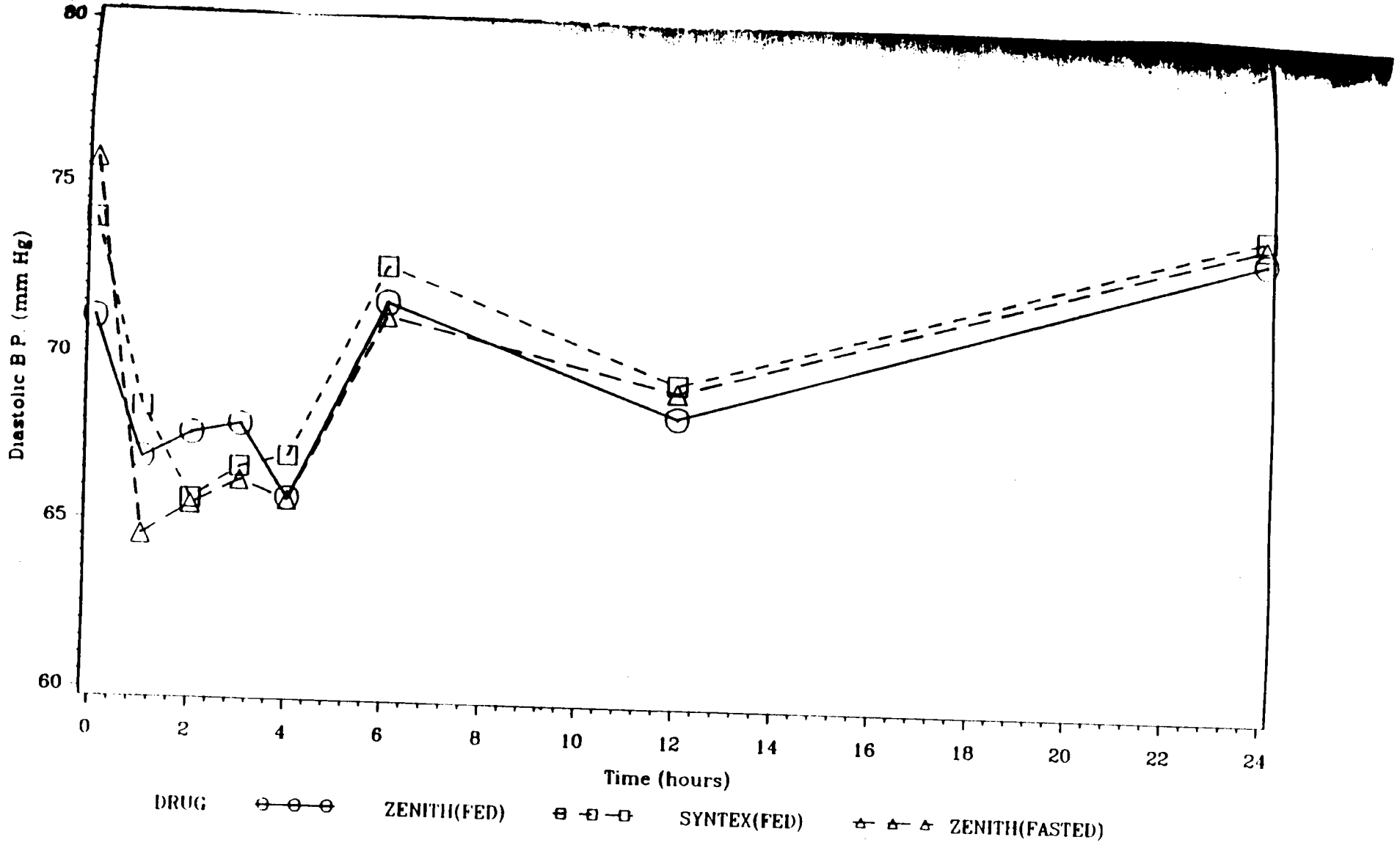


Figure 3

Mean Change in Diastolic Blood Pressure

N = 17

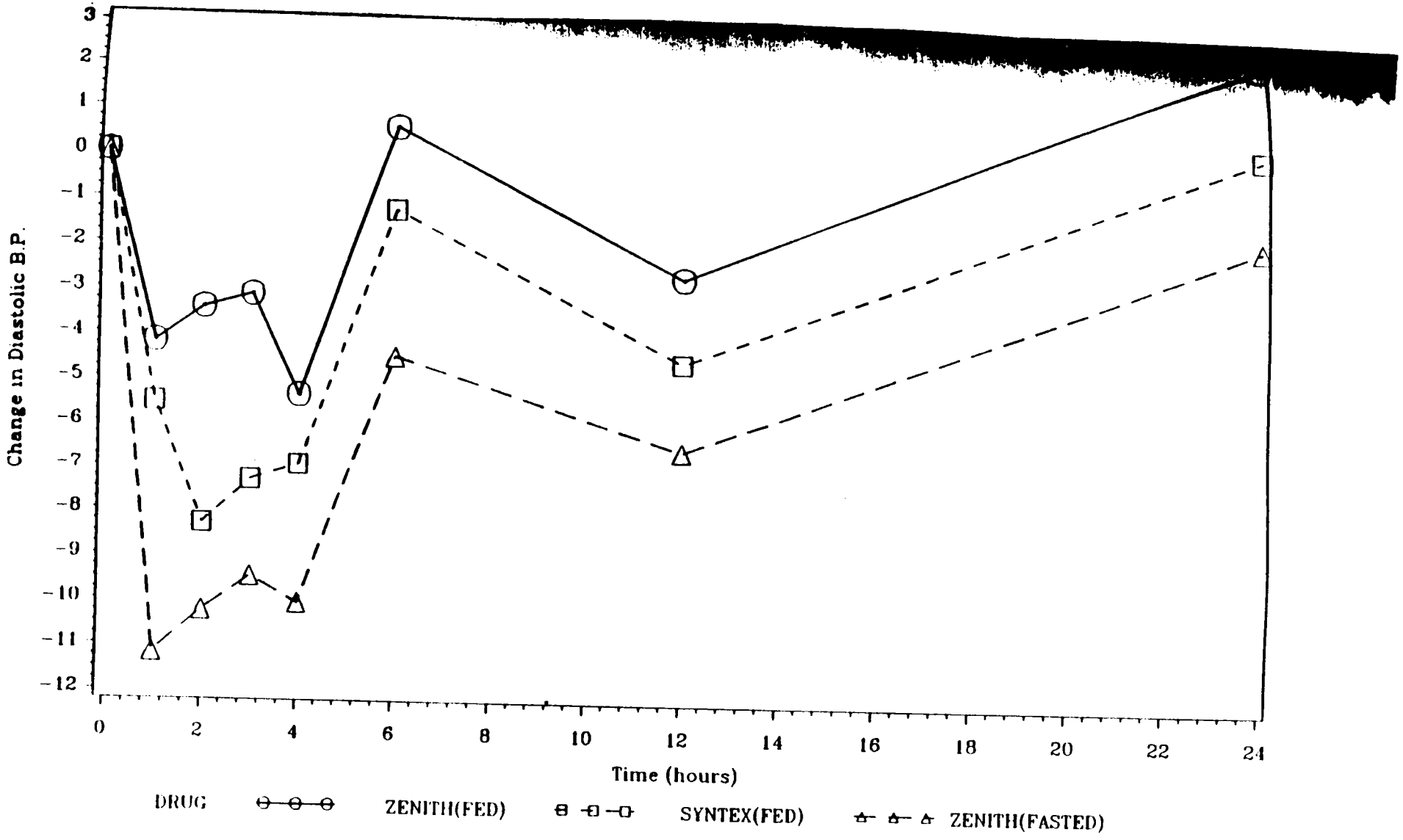


Figure 4

Mean Pulse

N=17

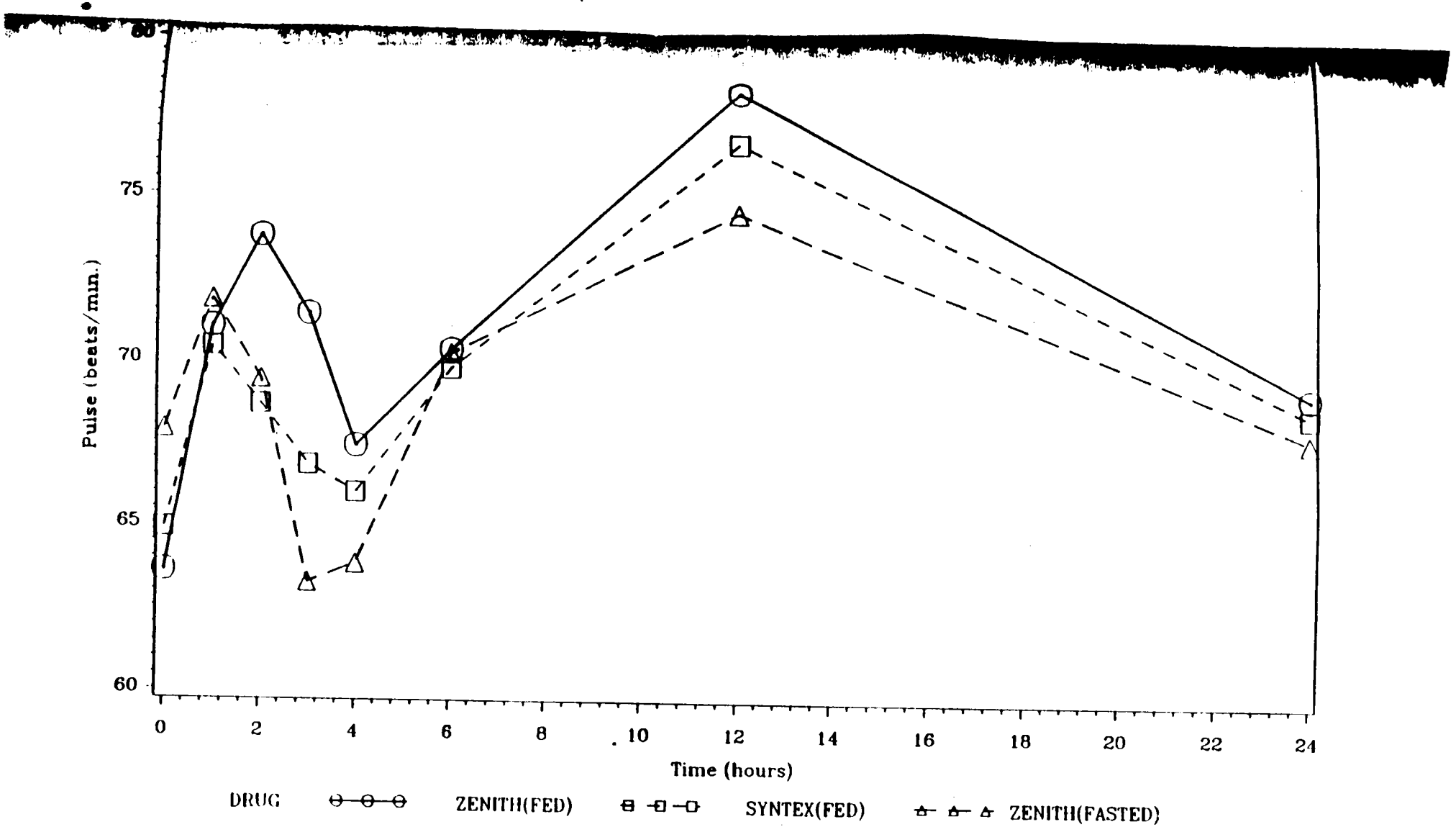


Figure 4—

Mean Change in Pulse

N=17